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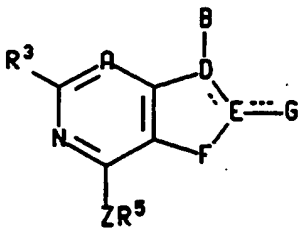
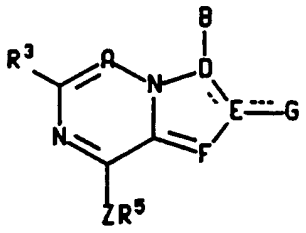
(54) Substituted heterocyclic derivatives as CRF antagonists

(57) Corticotropin-releasing factor (CRF) antagonists having the formula



I



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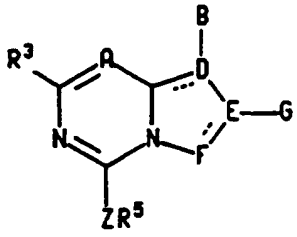

III

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wherein the dashed lines, A, B, D, E, F, Z, G, R^3, and R^5 are as defined below, and pharmaceutical compositions containing them.

Description

Background of the Invention

This invention relat s to certain pharmaceutically activ substituted heterocyclic derivatives, pharmaceutical compositions containing them and methods of administering them to subjects in need of their corticotropin releasing factor antagonist activity.

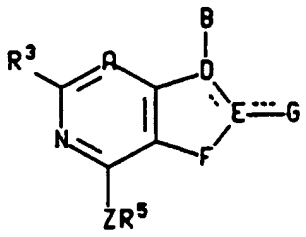
The substituted heterocyclic derivatives claimed in this case exhibit activity as corticotropin releasing factor CRF antagonists.

CRF antagonists are referred to in U.S. Patents 4,605,642 and 5,063,245, which relate, respectively, to peptides and pyrazolinones, and were issued, respectively, on August 12, 1986 and November 5, 1991. They are also referred to in the following: PCT Patent Application PCT/IB95/00439, which designates the United States and was filed on June 6, 1995; PCT Patent Application PCT/IB95/00373, which designates the United States and was filed on May 18, 1995; U.S. Patent Application 08/448,539, which was filed in the PCT on Nov. 12, 1993 and entered the U.S. national phase on June 14, 1995; U.S. Patent Application 08/481,413, which was filed in the PCT on November 26, 1993 and entered the U.S. national phase on July 24, 1995; and U.S. Patent Application 08/254,820, which was filed on April 19, 1995. All the foregoing patents and patent applications are incorporated herein by reference in their entireties.

The importance of CRF antagonists is discussed in the literature, e.g., as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference in its entirety. A recent outline of the different activities possessed by CRF antagonists is found in M. J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are effective in the treatment of a wide range of stress-related illnesses, such as depression, anxiety, headache, irritable bowel syndrome, inflammatory diseases, immune suppression, Alzheimers disease, gastrointestinal diseases, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, infertility, head trauma, stroke, and stress-induced infections in humans and animals.

Summary of the Invention

The present invention relates to compounds of the formula



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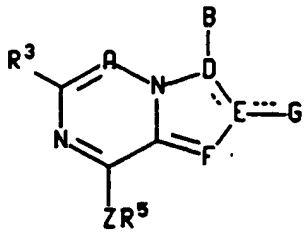

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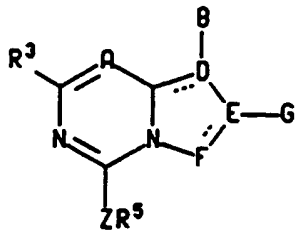


III

or a pharmaceutically acceptable salt thereof, wherein
the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is either double bonded to E in formulas I and II or double bonded to the adjacent carbon atom common to both fused rings in formula III, or D is CH and is single bonded to E in formulas I and II;

E is nitrogen, CH or carbon;

F is oxygen, sulfur, CHR^4 or NR^4 when it is single bonded to E and F is nitrogen or CR^4 when it is double bonded to E;

G, when single bonded to E, is hydrogen, C_1-C_4 alkyl, $-S(C_1$-C_4 alkyl), $-O(C_1$-C_4 alkyl), NH_2, $-NH(C_1$-C_4 alkyl) or $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), wherein each of the C_1-C_4 alkyl groups of G may optionally be substituted with one hydroxy, $-O(C_1$-C_2 alkyl) or fluoro group; G, when double bonded to E, is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D or F, is absent;

R^1 is hydrogen, C_1-C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, $-C(=O)O-(C_1$-$C_4)$alkyl, $-OC(=O)(C_1$-C_4 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-NHCO(C_1$-C_4 alkyl), -COOH, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_4 alkyl), -CN, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, $-OC(=O)(C_1$-C_6 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_6 alkyl), amino, $-NH(C_1$-C_2 alkyl), $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), $-N(C_1$-C_4 alkyl)$-CO-(C_1$-C_4 alkyl), $-NHCO(C_1$-C_4 alkyl), -COOH, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl);

$-NR^1R^2$ or $CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

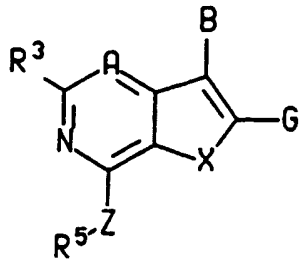
R^3 is hydrogen, C_1-C_4 alkyl, $-O(C_1$-C_4 alkyl), chloro, fluoro, brom , iodo, -CN, $-S(C_1$-C_4 alkyl) r $-SO_2(C_1$-C_4 alkyl) wh rein each of the (C_1-C_4 alkyl) moieties in th foregoing R^3 groups may ptionally be substituted with one substituent R^8 s lect d fr m hydroxy, fluoro and (C_1-C_2 alkoxy);

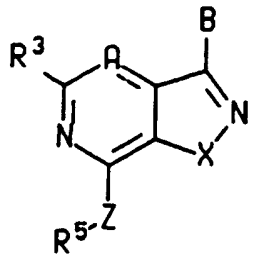
each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iod , hydroxy, cyano, amino, nitro, -O

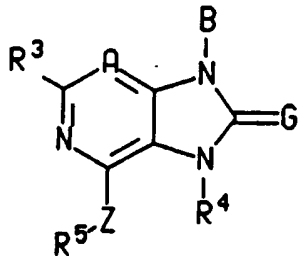
(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl, -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl), wher in each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moi ties in the for going R^4 gr ups may optionally contain ne or two double or triple bonds and may optionally be substituted with one or two substituents independently selected from hydroxy, amin , C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH_3, flu ro, chloro, C_1-C_3 thioalkyl, -CN, -COOH, -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl) and - NO_2;
R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein Z^4 is hydrogen, C_1-C_4 alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{12} wherein one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl and -O(C_1 -C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, -CF_3, -NO_2, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;
R^7 is hydrogen, C_1-C_4 alkyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, -O(C_1-C_4 alykl), -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -OCF_3, -CF_3, -CH_2OH or -CH_2O(C_1-C_2 alkyl);
R^{10} is hydrogen, hydroxy, methoxy or fluoro;
R^{11} is hydrogen or C_1-C_4 alkyl; and
Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), -NC(=O)(C_1-C_2 alkyl), NC(=O)O(C_1-C_2alkyl) or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14} can be cyano;

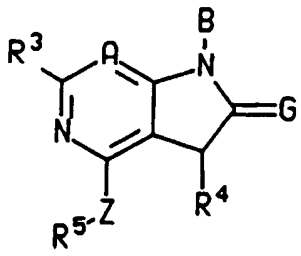
with the proviso that: (a) in the five membered rings of structures I, II and III, there can not be two double bonds adjacent to each other; and (b) when R^4 is attached to nitrogen, it is not halo, cyano or nitro.

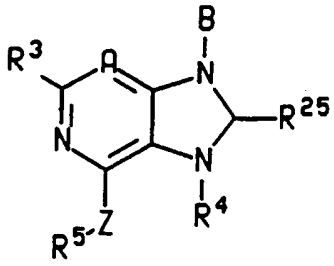
Examples of more specific embodiments of formula I, II and III are the following, wherein A, B, G, Z, R^3, R^4 and R^5 are defined as above, X is NR^4, O, S or CR^4 and R^{25} is hydrogen, (C_1-C_4)alkyl or CF_3.

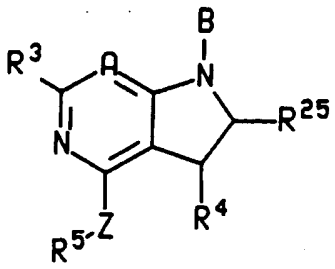


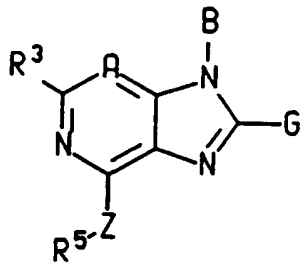


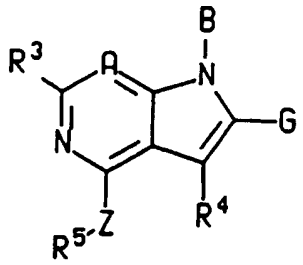


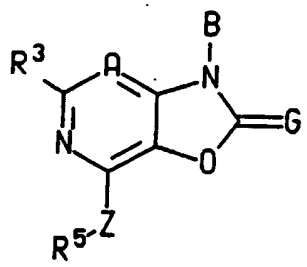


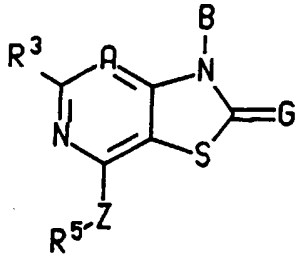


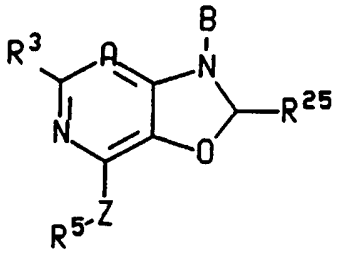


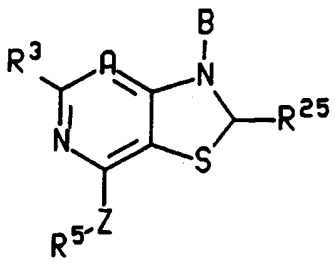


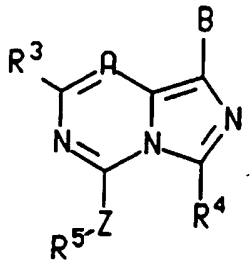


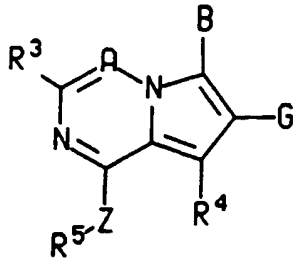


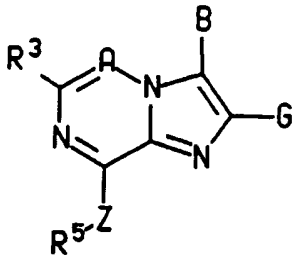


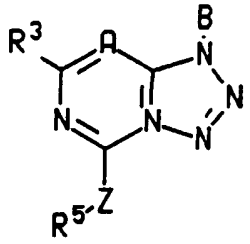


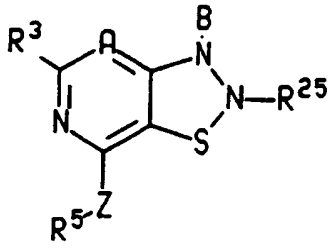












The compounds of formulas I, II and III may contain one or more chiral centers and may therefore occur in different isomeric forms. The invention includes all stereoisomers and diastereomers of such compounds of formulas I, II and III, including racemic and optically active mixtures thereof.

This invention also relates to the pharmaceutically acceptable acid and base addition salts of compounds of the formulas I, II and III. Examples of such pharmaceutically acceptable acid addition salts are the salts of hydrochloric acid, p-toluenesulfonic acid, maleic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, di-p-toluoyl tartaric acid, and mandelic acid. Examples of such pharmaceutically acceptable base addition salts are the salts of the alkali metals and alkaline earth metals.

More specific embodiments of this invention include compounds of the above formulas I, II and III wherein: R^1 is C_1-C_6 alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3, or C_1-C_4 alkoxy group and may optionally contain one double or triple bond; and R^2 is benzyl, C_1-C_6 alkyl, which may optionally contain one double or triple bond, wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl may optionally be substituted with one fluoro, CF_3, C_1-C_2 alkyl, C_1-C_2 alkoxy or chloro group.

Other more specific embodiments of the invention include compounds of formulas I, II and III wherein R^3 is methyl, ethyl, chloro or methoxy; R^4 is methyl, ethyl or trifluoromethyl; G is hydrogen, methyl, ethyl, or E=G is C=O, C=S; R^5 is phenyl, pyridyl, pyrimidyl which is substituted with mor than two substituents independently selected from C_1-C_4 alkyl, -O(C_1-C_4 alkyl), (C_1-C_4 alkyl)-O-(C_1-C_4 alkyl), CF_3, OCF_3, -CHO, (C_1-C_4 alkyl)-OH, CN, Cl, F, Br, I and NO_2, wherein each f the foregoing (C_1-C_4) alkyl groups may optionally contain one double or tripl bond.

Other mor specific mbodiments of the invention include compounds of the formulas I, II and III wher in A is N,

CH or CMe.

Examples f preferred compounds of this invention are:

2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;
1-(1- thylpropyl)-6-methyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
9-(1-ethylpropyl)-2-methyl-6-(2,4,6-trimethylphenylamino)-7,9-dihydro-purin-8-one;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-imidazo[4,5-c]pyridine;
1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one; and
1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one.

Examples of other compounds of this invention are:

[2,6-dimethyl-4-(2,4,6-trimethylphenoxy)-thien[3,2-d]pyrimidin-7-yl]diethylamine;
[2,6-dimethyl-4-(2,4,6-trimethylphenoxy)-thien[3,2-d]pyrimidin-7-yl]ethylpropylamine;
[2,6-dimethyl-4-(2,6-dimethyl-4-chlorophenoxy)-thien[3,2-d]pyrimidin-7-yl]diethylamine;
[2,6-dimethyl-4-(2,6-dimethyl-4-chlorophenoxy)-thien [3,2-d]pyrimidin-7-yl]ethyl-propylamine;
[2,6-dimethyl-4-(2,6-dimethyl-4-bromo-phenoxy)-thien[3,2-d]pyrimidin-7-yl]diethylamine;
[2,6-dimethyl-4-(2,6-dimethyl-4-bromophenoxy)-thien[3,2-d]pyrimidin-7-yl]ethyl-propylamine;
[2-methyl-4-(2,4,6-trimethylphenoxy)-thien[3,2-d]pyrimidin-7-yl] diethyl-amine;
3-(1-ethylpropyl)-2,5-dimethyl-7-(2,4,6-trimethylphenoxy)-thien [2,3-c]pyridine;
[3-(1-ethylpropyl)-2,5-dimethyl-thien[2,3-c]pyridin-7-yl]-(2,4,6-trimethylphenyl)-amine;
3-(1-ethylpropyl)-2,5-dimethyl-7-(2,4,6-trimethylphenoxy)-furo[2,3-c]pyridine;
[3-(1-ethylpropyl)-2,5-dimethyl-furo[2,3-c]pyridin-7-yl]-(2,4,6-trimethylphenyl)-amine;
[1-(1-ethylpropyl)-2,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1H-pyrrolo[3,2-c]pyridine;
[1-(1-ethylpropyl)-2,6-dimethyl-1H-pyrrolo[3,2-c]pyridin-4-yl]-(2,4,6-trimethylphenyl)amine;
[1-(1-ethylpropyl)-3,6-dimethyl-1H-pyrrolo[3,2-c]pyridin-4-yl]-(2,4,6-trimethylphenyl)amine;
[1-(1-ethylpropyl)-6-methyl-1H-pyrrolo[3,2-c]pyridin-4-yl]-(2,4,6-trimethylphenyl)-amine;
[1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-pyrazolo[4,3-c]pyridine;
[1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1H-pyrazolo[4,3-c]pyridine;
[1-(1-ethylpropyl)-3,6-dimethyl-1H-pyrazolo[4,3-c]pyridin-4-yl]-(2,4,6-trimethylphenyl)amine;
[1-(1-ethylpropyl)-6-methyl-1H-pyrazolo[4,3-c]pyridin-4-yl]-(2,4,6-trimethylphenyl)-amine;
[3-(1-ethylpropyl)-5-methylisoxazolo[4,5-d]pyrimidin-7-yl]-(2,4,6-trimethylphenyl)-amine;
[3-(1-ethylpropyl)-5-methylisoxazolo[5,4-c]pyridin-7-yl]-(2,4,6-trimethylphenyl)-amine;
[3-(1-ethylpropyl)-5-methylisothiazolo[4,5-d]pyrimidin-7-yl]-(2,4,6-trimethylphenyl)amine;
[3-(1-ethylpropyl)-5-methylisothiazolo[5,4-c]pyridin-7-yl]-(2,4,6-trimethylphenyl)-amine;
diethyl-[5-methyl-7-(2,4,6-trimethylphenoxy)-isothiazolo[5,4-c]pyridin-3-yl]amine;
N3,N3-diethyl-[5-methyl-N7-(2,4,6-trimethylphenyl)-isothiazolo[5,4-c]pyridin-3,7-diamine;
N3,N3-diethyl-[5-methyl-N7-(2,4,6-trimethylphenyl)-isoxzolo [5,4-c] pyridin-3,7-diamine;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-[1,2,3]triazolo[4,5-c]pyridine;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenylsulfanyl)-1H-[1,2,3]triazolo[4,5-c]pyridine;
3-(1-ethylpropyl)-1,5-dimethyl-7-(2,4,6-trimethylbenzyl)-1H-pyrrolo[2,3-c]pyridine;
3-(1-ethylpropyl)-1,5-dimethyl-7-(2,4,6-trimethylbenzyl)-1H-pyrrolo[3,2-d]pyrimidine;
5-(1-ethylpropyl)-3,6-dimethyl-1-(2,4,6-trimethylphenoxy)-pyrrolo[1,2-c]pyridine;
N6,N6-diethyl-3,7-dimethyl-N1-(2,4,6-trimethylphenyl)-pyrrolo[1,2-a]pyrazine-1,6-diamine;
6-(1-ethylpropyl)-3,7-dimethyl-1-(2,4,6-trimethylphenoxy)-pyrrolo[1,2-a]pyrazine;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-[1,2,3]triazolo[4,5-c]pyridine;
diethyl-[3,7-dimethyl-N1-(2,4,6-trimethylphenoxy)-pyrrolo[1,2-a]pyrazin-6-yl]-amine;
[1-(ethylpropyl)-3,7-dimethyl-imidazo[1,5-c]pyrimidin-5-yl]-(2,4,6-trimethylphenyl)amine;
7-Bromo-1-(1-ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-[1,2,3]triazolo[4,5-c]pyridine;
1-(1-Ethyl-propyl)-6,7-dimethyl-4-(2,4,6-trimethyl-phenoxy)-1H-[1,2,3]triazolo[4,5-c]pyridine;
1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1,3-dihydropyrrolo-[3,2-c]pyridin-2-one;
1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-imidazo[4,5-c]pyridin-2-ylamine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(2,4,6-trimethyl-ph noxy)-1,3-dihydro-pyrrol [3,2-c]pyridin-2-one;
1-(1-Ethyl-propyl)-3,3,6-trim thyl-4-(2,4,6-trimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
1-(1-Ethyl-propyl)-3,3,6-trimethyl-4-(2,4,6-trimethyl-phenoxy)-2,3-dihydro-1 H-pyrrolo[3,2-c]pyridine;

1-(1-Ethyl-propyl)-3,6-dimethyl-4-(2,4,6-trimethyl-phen xy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-2-methoxy-3,6-dimethyl-4-(2,4,6-trim thylphenoxy)-1H-pyrrolo[3,2-c]pyridin ;
[1-(1-Ethyl-propyl)-6-methyl-1H-[1,2,3]triaz lo[4,5-c]pyridin-4-yl]-(2,4,6-trimethylphenyl)-amine;
4-(4-Bromo-2,6-dimethyl-phenoxy)-1-(1-ethyl-pr pyl)-6-methyl-1H-oxazolo[5,4-c]pyridin-2-one;
1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-oxazol [5,4-c]pyridin-2-one;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-chloro-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-bromo-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-i-propyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-t-butyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-ethyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-propyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1 -(1-Ethyl-propyl)-3,6-dimethyl-4-(4-trifluoro-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-methoxymethyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-hydroxymethyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c] pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-formyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(2-bromo-4-i-propyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3,6-dimethyl-4-(2,4-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
1-(1-Ethyl-propyl)-3-ethyl-6-methyl-4-(2,6-dimethyl-4-chloro-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
2-[4-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl]-butan-1-ol;
2-[4-(4-bromo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl]-butan-1-ol;
2-[4-(4-i-propyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl]-butan-1-ol;
2-[4-(4-Ethyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrrolo [3,2-c]pyridin-1-yl]-butan-1-ol;
2-[4-(4-trifluoromehtyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl]-butan-1-ol;
2-[4-(2-bromo-4-i-propyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl]-butan-1-ol.

Whenever reference is made herein to C_1-C_6 alkyl, a straight or branched chain alkyl of one to six carbon atoms is meant, such as methyl, ethyl, isopropyl, t-butyl or hexyl.

Whenever R^2 or R^5 is a heterocyclic group, attachment of the group is through a carbon atom.

Whenever reference is made herein to C_1-C_4 alkyl or C_1-C_6 alkyl which "may contain one double or triple bond" in the definitions of R^1 and R^4, it is understood that at least two carbons are present in the alkyl for one double or triple bond.

Whenever reference is made herein to halo or halogen, fluoro, chloro, bromo or iodo is meant unless indicated otherwise.

This invention also relates to a pharmaceutical composition for the treatment or prevention of (a) a disorder, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal disorders such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated with psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; osteoporosis; psychosocial dwarfism; and hypoglycemia in a mammal, including a human, comprising an amount of a compound of the formula I, II or III, or a pharmaceutically acceptable salt thereof, that is effectiv in the treatment or prevention of such disorder, and a pharmaceutically acceptable carrier.

This invention also relates to a pharmaceutical composition for the prev ntion or pr mature births in a mammal, including a human, comprising an amount of a compound of the formula I, II r III, or a pharmaceutically acceptable

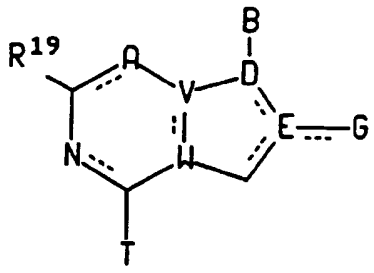
salt thereof, that is effective in the pr v ntion of such disorder, and a pharmaceutically acc ptable carrier.

This inv ntion further includes a method for the treatment or prevention of (a) a disord r, the treatment of which can b effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitator by CRF, or (b) a disorder s lected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated with psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome; bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in a mammal, including a human, comprising administering to a subject in need of said treatment an amount of a compound of the formula I, II or III, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

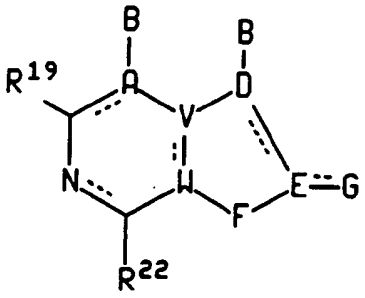
This invention also relates to a method of preventing premature births in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, II or III, or a pharmaceutically acceptable salt thereof, that is effective in preventing such disorder.

Detailed Description of the Invention

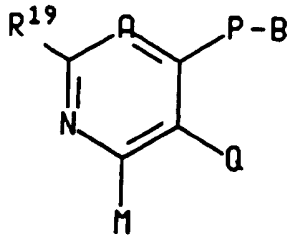
The following compounds having the formulas IV, V and VI are useful as starting materials and intermediates in the synthesis of compounds of the formulas I, II and III.



IV



V

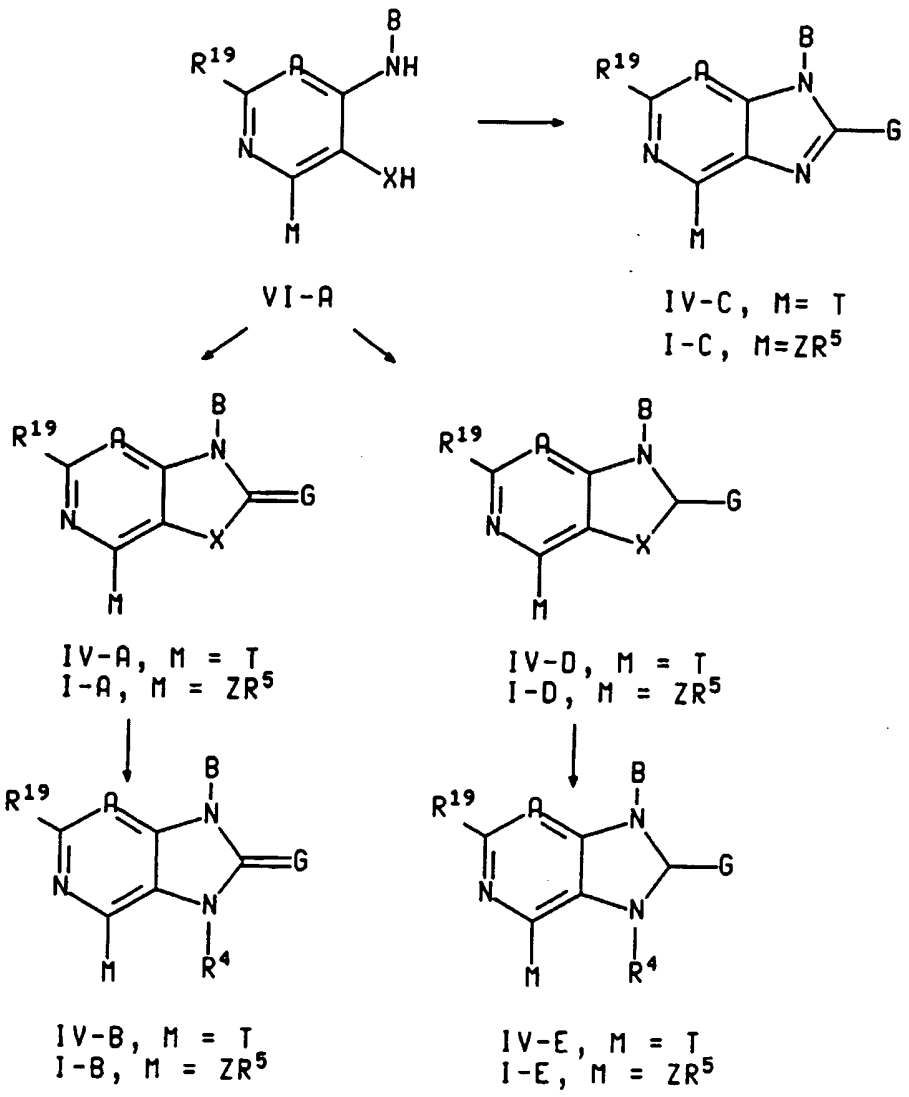


VI

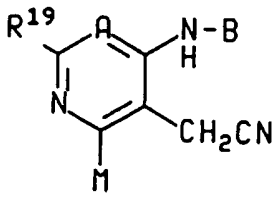
In the above compounds of formulas IV, V and VI, R^{19} is (C_1-C_4)alkyl, fluoro, chloro, bromo or iodo, T is chloro, bromo, iodo, -$OCOCF_3$ or -OSO_2CF_3, M is T or ZR^5, R^{22} is OH or NH_2, P is NH, CHCN or CHCOO(C_1-C_4 alkyl), Q is -NH_2, -CH_2COO(C_1-C_4alkyl), CH_2CN, -OH or -SH, V and W are, independently, C or N, but cannot both be N, and A, B, D, E, F and G are defined as above.

Methods of preparing the compounds and compositions of this invention are described below. In the discussion and reaction schemes that follow, R^1 through R^5, R^7 through R^{14}, R^{19}, R^{25} A, B, D, E, F, G, X, the dashed lines and structural formulas I, II, III, IV, V and VI, unless otherwise indicated, are defined as above.

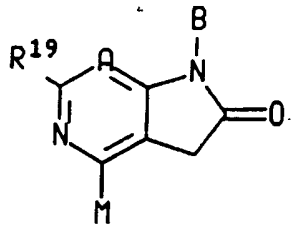
Scheme 1


VI-A
IV-C, M= T
I-C, M=ZR5
IV-A, M = T
I-A, M = ZR5
IV-D, M = T
I-D, M = ZR5
IV-B, M = T
I-B, M = ZR5
IV-E, M = T
I-E, M = ZR5

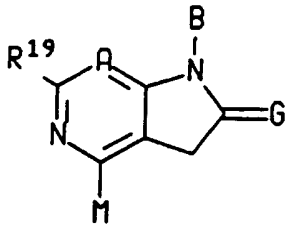
Scheme 2



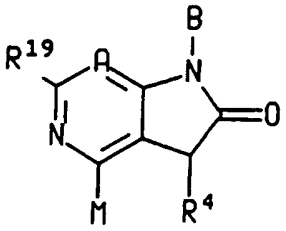
VI-B



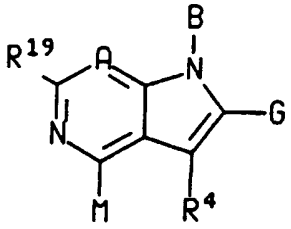
IV-F, M=T;
I-F, M=ZR^5



IV-G, M=T;
I-G, M=ZR^5

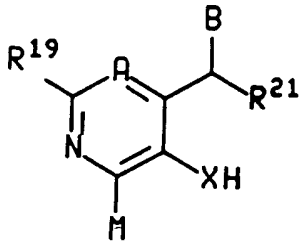


IV-H, M=T;
I-H, M=ZR^5



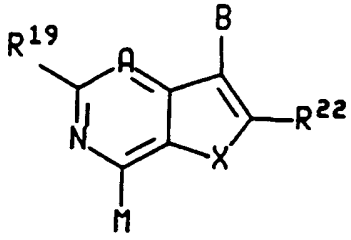
IV-J, M=T;
I-J, M=ZR^5

Scheme 3

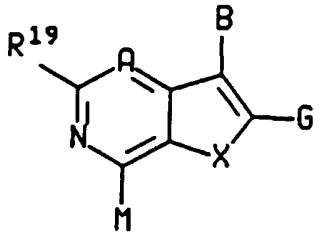


VI-C

M=ZR^5 or halo;
X=O, S, NH or CHCN
R^{21}=CN or -COO(C_1-C_4alkyl)

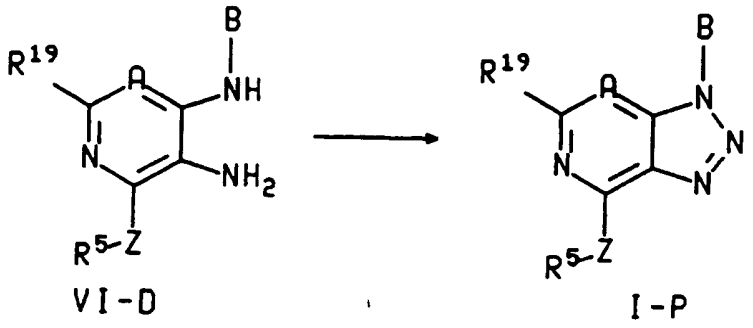


IV-K, M=T;
I-K, M=ZR^5
R^{22}=OH or NH_2



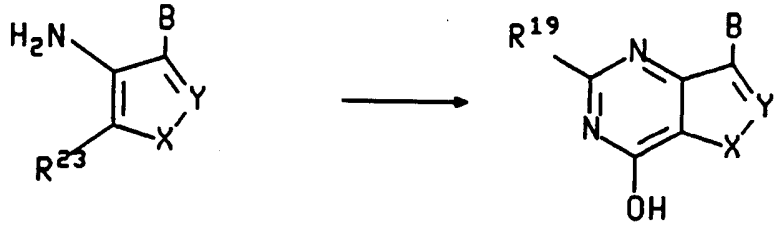
IV-L, M=T;
I-L, M=ZR^5

Schem 4



VI-D I-P

Scheme 5



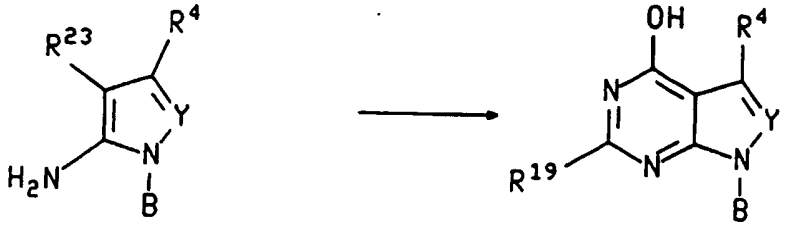
VII V-M

X=NH or N(C_1-C_4 alkyl);

Y=N, CH or C(C_1-C_4 alkyl);

R^{23}=-CN, -$CONH_2$ or -COO(C_1-C_4 alkyl)

Schem 6

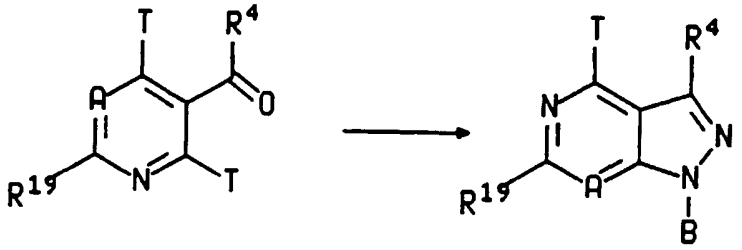


VIII V-N

R^{23}=-CN, $-CONH_2$ or $-COO(C_1-C_4$ alkyl);

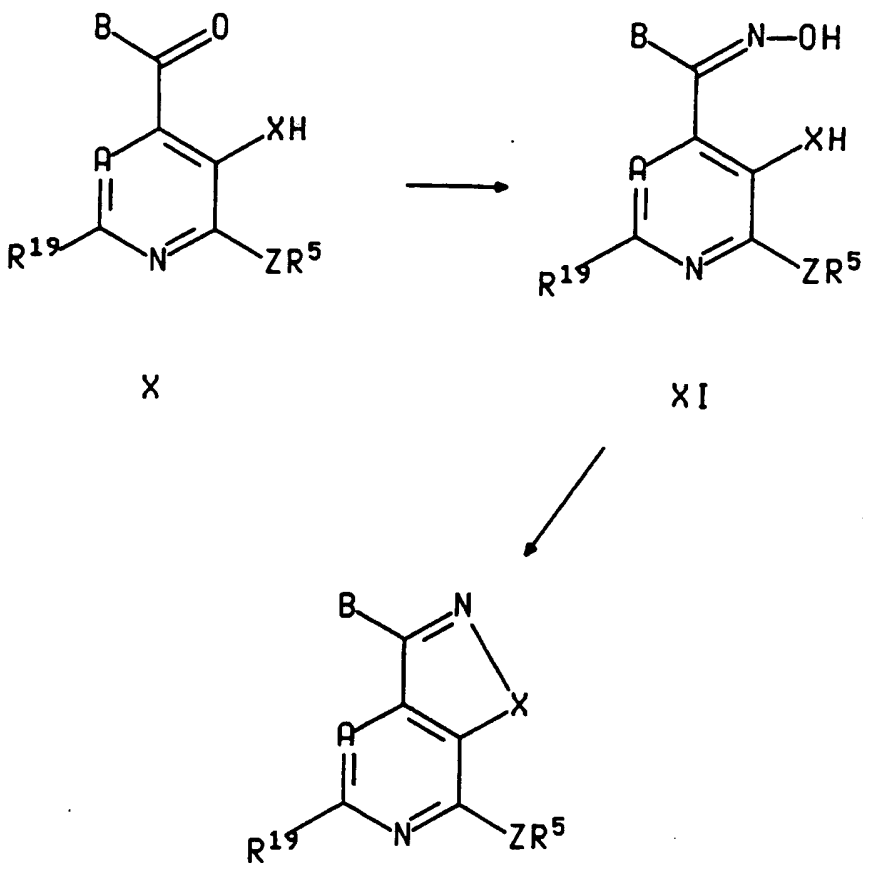
Y=N or C-G

Scheme 7



IX IV-O

Schem 8



X XI I-Q

Compounds of formulas I, II, and III wherein R^3 is C_1-C_4alkyl, fluoro, chloro, bromo, or iodo (hereinafter R^{19}) may be prepared by reaction of a compound of formula IV, wherein T is Cl, Br, I, -O-$COCF_3$, -OSO_2CF_3, V and W are, independently, C or N and V and W are not both N, and A, T, D, E, F, and G are defined as above with reference of formulas I, II, and III, with a compound of formula R^5ZH wherein Z and R^5 are as defined above. This reaction is generally carried out with or without a solvent, in the presence of a base, at a temperature from about 0°C to about 270°C, and at a pressure between about 1 atmosphere and 300 psi. Suitable solvents include organic solvents such as tetrahydrofuran (THF), acetonitrile, dimethylsulfoxide (DMSO), acetone, C_2-C_{15} alcohols, chloroform, dioxane, chlorobenzene, benzene, toluene, xylene, sulfolane, pyridine, quinoline, 2,4,6-trimethylpyridine, acetamide, di-(C_1-C_2)alkylacetamide, or 1-methyl-2-pyrrolidinone (NMP).

When Z is NH, an excess of R^5ZH may be used both as a reagent and as a base. Examples of bases other than R^5ZH that may be used include potassium carbonate, sodium hydride, potassium hydride, sodium (C_1-C_4) alkoxides, potassium (C_1-C_4) alkoxides, sodium, sodium amide, tri-[(C_1-C_6) alkyl]amines, organolithium or organosodium compounds such as n-butyllithium, s-butyllithium, t-butyllithium, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium diisopropylamide or sodium bis(trimethylsilyl)amide, and organometallic bases such as Grignard reagents. This reaction is generally carried out in an appropriat solvent (_.g., THF, dioxan , sulfolane, DMSO or NMP, with or without an additinal catalyst such as a copper halide, oxide or sulfate (e.g., CuI, CuBr, Cu_2O, CuCl, $CuSO_4$ CuI_2, $CuBr_2$, $CuC1_2$ or Cu(O)), a Pd(0) salt such as tetrakis(triphenylphosphine)palladium ($Pd(PPH_3)_4$), a Pd(II) salt such as palla-

dium diacetate ($Pd(OAc)_2$) or racemic or (R)- or (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), at temperature from about room temperatur to about 270°C.

When Z is O r S, a base which is capable of d protonating R^5ZH may be used, such as potassium carbonate, sodium carbonate, sodium, sodium amide, an alkali metal hydride such as sodium or potassium hydrid , a sodium C_1-C_4 alkoxide, a potassium C_1-C_4 alkoxide, sodium amide, a tri-(C_1-C_6alkyl)amine or an organometallic base such as n-butyllithium, s-butyllithium, t-butyllithium, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium diisopropylamide or sodium bis(trimethylsilyl)amide. The reaction temperature can range from about 0° C to about 180°C and is preferably from about 50°C to about 140°C. Suitable solvents include DMSO, THF, sulfolane, dioxane and NMP.

When Z is CHCN or CHCOO(C_1-C_4 alkyl), a base that is capable of deprotonating R^5ZH may be used, such as an alkali metal hydride (e.g., sodium or potassium hydride), a sodium C_1-C_4 alkoxide or an organometallic base such as n-butyllithium, s-butyllithium, t-butyllithium, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium diisopropylamide or sodium bis(trimethylsilyl)amide, in an appropriate solvent, e.g., a solvent selected from THF, DMSO, dioxane, methylene chloride (CH_2Cl_2), chloroform ($CHCl_3$), toluene, xylene, benzene and C_1-C_6 alkanols.

Compounds of the formulas I, II and III wherein Z is $CR^{13}CN$, CHR^{13}, N(C_1-C_4 alkyl), NC(=O)(C_1-C_2 alkyl) and NC(=O)O(C_1-C_2 alkyl) may be prepared as described below, using methods that are well known in the art.

When Z is $CR^{13}CN$, compounds of formulas I, II, and III may be prepared by reaction of the corresponding compounds wherein Z is CHCN with a base such as an alkali metal hydride such as sodium or potassium hydride, n-butyllithium, s-butyllithium, t-butyllithium, lithium diisopropylamide, lithium bis(trimethylsilyl)amide or sodium diisopropylamide, followed by reacting with a compound of the formula $R^{13}L$ wherein L is a leaving group such as I, Br, Cl, mesylate (OMs) or tosylate (OTs).

Compounds of the formulas I, II and III wherein Z is CHR^{13} may be prepared by acid hydrolysis (using, e.g., 85% phosphoric acid) of the corresponding compounds wherein Z is $CR^{13}CN$, followed by decarboxylation upon heating. Further alkylation in the presence of base and a compound of the formula and $R^{14}L$, wherein L is defined as above, will yield the corresponding compounds of formulas I, II and III wherein Z is $CR^{13}R^{14}$.

When Z is N(C_1-C_4 alkyl), compounds of the formulas I, II and III may be prepared by reaction of the corresponding compounds wherein Z is NH with a base, followed by reaction with a compound of the formula (C_1-C_4 alkyl)-L, wherein L is defined as above. Bases such as lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium diisopropylamide may also be used.

When Z is NC(=O)(C_1-C_2 alkyl) or NC(=O)O(C_1-C_2 alkyl), compounds of the formulas I, II, and III may be prepared by reaction of the corresponding compounds wherein Z is NH with a compound of the formula [(C_1-C_2 alkyl)-C(=O)]$_2$O, (C_1-C_2 alkyl)-C(=O)(Cl) or (C_1-C_2 alkyl)-O-C(=O)(Cl) in the presence of base such as a tri(C_1-C_6 alkyl)amine or pyridine.

Compounds of formulas I, II, and III, wherein Z and R^5 are defined with reference formulas I, II, and III above and R^3 is -O-(C_1-C_4 alkyl) or -S-(C_1-C_4 alkyl) (hereinafter R^{20}), may be prepared by reacting the corresponding compounds of the formulas I, II, and III, wherein R^3 is chloro, bromo, OTs or iodo, with a nucleophile of the formula $R^{20}H$, wherein $R^{20}H$ is an alkanol or an alkane thiol, optionally in the presence of an organic or inorganic base. Suitable bases include sodium, sodium hydride, potassium hydride, lithium diisopropylamide, lithium bis(trimethylsilyl)amide and sodium diisopropylamide.

Compounds of the formulas I, II, or III wherein R^3 is fluoro may be prepared by reacting the corresponding compounds wherein R^3 is chloro, bromo, iodo, -OCOCF$_3$, or -OSO$_2$CF$_3$ with tetrabutylammonium fluoride, potassium fluoride or another fluoride agent, using procedures well known to those skilled in the art. Compounds of the formulas I, II, or III wherein R^3 is CN may be prepared by reacting the corresponding compounds of formulas I, II, or III wherein R^3 is chloro, bromo, iodo, -OCOCF$_3$, or-OSO$_2$CF$_3$ with sodium cyanide, potassium cyanide, copper cyanide or other cyanide agent, using methods well known to those of skill in the art.

When R^{22} is OH, compounds of formula IV may be prepared from compounds of formula V. When T is Cl, the compound of formula IV may be prepared by heating a compound of formula V with an excess of $POCl_3$, $POCl_3$/PCl_5 or PCl_5 at a temperature from about 80°C to about 150°C, preferably at about the reflux temperature. When T is Cl, Br, or I, the compound of formula IV may be prepared by reacting the corresponding compound of formula IV wherein T is -OCOCF$_3$ or -OSO$_2$CF$_3$, preferably -OSO$_2$CF$_3$, with a sodium, potassium, or lithium halide in a suitable solvent such as sulfolane, DMSO or 1-methyl-2-pyrrolidinone. Compounds of formula IV wherein T is -OCOCF$_3$ or -OSO$_2$CF$_3$ may be prepared by reacting a compound of formula V with ($CF_3CO)_2O$, ($CF_3SO_2)_2O$, CF_3SO_2Cl, or CF_3COCl, with or without a base. Suitable bases include tri-(C_1-C_6 alkyl)amines and sodium and potassium carbonates. When R^3 is chloro, bromo, iodo, -OCOCF$_3$, or -OSO$_2$CF$_3$, it is preferable for R^3 and T to be the same.

When R^{22} is NH_2, compounds of the formula IV may be prepared by reacting a compound of the formula V with a compound of the formula (C_1-C_4 alkyl)-O-N=O and a copper (II) halide in an appropriate solvent such as acetonitrile, aceton , toluene, methylene chloride or dichl roethan , at a temperature from about room temperature to about the reflux temperature. This reaction is preferably carried ut in acetonitrile at the reflux t mperatur .

Alternativ ly, as shown in Scheme I, compounds of th f rmulas I-A, I-C and I-D may b pr par d from compounds of the f rmula VI-A. Referring to Scheme 1, reaction of a compound of the formula VI-A (wherein M is T or ZR^5, T is

Cl, Br, I, OTs or -OCOCF$_3$, X is O, NH, NR^4, or S, and A, B, and R^{19} are defined as abov) with phosgene or its equivalent (_g., diphosgene r triphosg n), thi phosgene, or CNBr, in the presence of a bas such as a tri-(C_1-C_4) alkylamine or sodium hydride, in an appropriat solvent (e.g., methylene chloride, chlor form or THF) in the presenc of a tri(C_1-C_4 alkyl)amine, will yield compounds of the formula IV-A wherein M is T and G is O, S, or NH, r the corresponding compounds of the formula I-A wherein M is ZR^5. Compounds of formula I-C and IV-C may be pr pared by heating compounds of formula VI-A with a compound of the formula (C_1-C_4 alkyl)-C-[O(C_1-C_2 alkyl)]$_3$ or HC[O-(C_1-C_2) alkyl]$_3$ in the presence of a catalytic amount of acid (e.g., p-toluene sulfonic, conc. sulfuric acid or gaseous hydrogen chloride), in an appropriate solvent such as toluene, benzene or xylene, under a Dean-Stark trap. Compounds of the formula I-D wherein G is hydrogen or C_1-C_4 alkyl may be prepared by heating a compound of the formula GCHO or GH(OMe)$_2$ in the presence of an acid catalyst. Alkylation of compounds of the formula I-A or I-D wherein X is NH with a compound of the formula R^{4}L wherein L is a leaving group, as defined above, or wherein R^{4}L is (C_1-C_4)$_2$SO$_2$, in the presence of a base that is capable of deprotonating NH such as sodium hydride or butyllithium, yields the corresponding alkylated derivative of the formula I-B or I-E, respectively. Compounds of formulas IV-A, IV-B, IV-C, IV-D and IV-E wherein M is T may be converted to the corresponding compounds of formulas I-A through I-E wherein M is ZR^5 by the methods described above for converting compounds of the formula IV into compounds of the formulas I, II and III.

Compounds of the formula I-F may be prepared, as illustrated in Scheme 2, by reacting the corresponding compounds of the formula VI-B (wherein M, X, A, B, and R^{19} are defined as in the preceding paragraph) with a base that is capable of deprotonating NH (such as sodium hydride, potassium hydride, or an organometallic base such as lithium diisopropylamide, lithium bis(trimethylsilyl)amide or sodium diisopropylamide) in an appropriate solvent, e.g., a solvent selected from THF, dioxane, DMSO, benzene, toluene, methylene chloride and chloroform. Alternatively, heating a compound of the formula VI-B in the presence of an acid (e.g., p-toluenesulfonic acid, aqueous phosphoric acid concentrated sulfuric acid or gaseous hydrogen chloride), in an appropriate solvent such as toluene, benzene or xylene, will yield the corresponding compound of formula I-F. Alkylation of compounds of formula I-F with a compound of the formula R^{4}L, defined as above, in the presence of a base such as sodium hydride, potassium hydride, or an organometallic base such as lithium diisopropylamide, lithium bis(trimethylsilyl)amide or sodium diisopropylamide, in an appropriate solvent such as THF or dioxane, yields the corresponding compounds of formula I-H.

Compounds of the formula I-J wherein G is chloro or trifliate may be prepared by heating the corresponding compounds of formula I-H with $POCl_3$, with or without PCl_5 or $(Tf)_2O$ (wherein Tf is triflate), respectively. Displacement of the chloro or OTf group of a compound of formula I-G with a nucleophile will yield the corresponding compound of formula I-J wherein G is defined for formula I. Compounds of the formula I-G wherein G is S may be prepared by reacting the corresponding compounds of formula I-F with Lawessen's reagent or P_4S_{10}. Compounds of the formula I-J wherein G is H may be prepared by reduction of the corresponding compounds of formula I-F or I-H with lithium aluminum hydride ($LiAlH_4$) or borane methyl sulfide complex (BH_3•DMS), followed by acid hydrolysis. Organometallics addition (using, e.g., GU, GMgBr or GMgl), followed by acid hydrolysis, employing methods well known in the art, will provide compounds of formula I-J wherein G is (C_1-C_4) alkyl.

Deprotonation of I-H with a base such as NaH in HMPA, followed by quenching with a (C_1-C_4 alkyl)$_2$SO$_2$- or C_1-C_4 alkyl containing electrophile, will yield a compound of formula I-J wherein G is O-(C_1-C_4 alkyl).

Compounds of formula I-K wherein R^{22} is -OH or -NH_2 may be prepared by reacting the corresponding compounds of the formula VI-C with a base or acid as a catalyst to effect ring cyclization as shown in Scheme 3. For example, a base that is capable of deprotonating of the XH of formula VI-C, such as sodium hydride, potassium hydride, or an organometallic base such as lithium diisopropylamide, lithium bis(trimethylsilyl)amide, or sodium diisopropylamide, can be reacted with the appropriate compound of formula VI-C in an appropriate solvent such as THF, dioxane, toluene, DMSO, NMP, a C_1-C_5 alcohol or acetonitrile, at temperature from about 0°C to about 180°C, to effect ring formation. Alternatively, this reaction may be performed by heating the compound of formula VI-C in the presence of an acid catalyst or an appropriate Lewis acid such as aluminium chloride (AlCl3) or borontrifluoride ethyl ether complex (BF_3•Et_2O, wherein Et=ethyl).

Conversion of compounds of the formula I-K wherein R^{22} is hydroxy into the corresponding compounds of formula I-L may be accomplished by the method described above for transformation of compounds of the formula I-F into compounds of the formula I-J.

Compounds of the formula I-P may be prepared, as shown in Scheme 4, by reacting compounds of the formula VI-D with sodium nitrite in 48% hydrogen bromide in the presence of cuprous bromide or bromine at a temperature from about 0°C to about the reflux temperature. Preferably, the reaction is carried out at about 0°C for about thirty minutes, and then at mild reflux.

As shown in schemes 5 and 6, compounds of the formulas V-M and V-N, wherein Y is N or C(C_0 - C_4) alkyl, may be prepared by heating, respectively, compounds of the formula VII and VIII, wherein R^{23} is CN, X is O, S, NH or N (C_1-C_4 alkyl), and Y is CH, N r C(C_1-C_4 alkyl), with a compound of formula acid (R^{24}CO)$_2$O in R^{2}4COOH, at temperatur from about 25°C to about 120°C, pr ferably at the reflux t mperature of the reaction mixture. Th above formed compounds wherein R^{19} is hydrogen, C_1-C_6 alkyl or hydroxy may be heated in aqueous acid to give compounds of

formula V-M or V-N. Appropriate acids includ 85% phosph ric acid , hydrochloric acid, sulfuric acid and ac tic acid. Eighty-five perc nt phosphoric acid is pref rr d. The reaction is carried out at a temperatur from about 25°C to about 180°C, preferably from about 100°C to about 150°C.

Compounds of the formulas V-M and V-N (wherein Y is N) may be pr par d, as shown in Schemes 5 and 6, by heating compounds of the formulas VII and VIII, r spectively, [wherein R^{23} is $CONH_2$ r $COO(C_1$-C_4 alkyl), X is O, S, NH or N(C_1-C_4 alkyl) and Y is CH or C(C_1-C_4 alkyl)], with a compound of the formula $C_{19}CONH_2$ wherein R^{19} is as defined above. This reaction can be conveniently carried out in the absence of a solvent at temperatures ranging from about 100°C to about 250°C.

Compounds of formula IV-O may be prepared by reacting the corresponding compounds of formula IX wherein A, T, R^{19} and R^4 are defined as above with $BNHNH_2$ in an appropriate solvent as shown in Scheme 7. Suitable solvents include C_1-C_5 alcohols, acetonitrile, toluene, chlorobenzene, xylene, toluene, dioxane, chloroform and methylene chloride, preferably in i-propanol or acetonitrile.

Compounds of the formula I-Q can be prepared as illustrated in Scheme 8. Compounds of formula XI wherein B is $CR^1R^2R^{10}$ or CN, X is O, S, NH, N(C_1-C_4 alkyl), and R^{10}, A, Z, R^5 are defined as above may be prepared by reacting compounds of formula X with hydroxylamine•HCl in a mixture of a solvent selected from C_1-C_5 alcohols, CH_3CN, acetone, dioxane and water, with or without sodium acetate, at a temperature from about room temperature to about 120°C, preferably at about the reflux temperature. Compounds of formula XI can then be reacted with an appropriate agent convert the hydroxy group of the oxime into a good leaving group such as -OAc, $-OCOCF_3$, $-OSO_2CF_3$, $-OSO_2CH_3$ or $-OSO_2C_6H_5CH_3$ (p-tosylate). Examples of such appropriate agents are acetic anhydride, trifluoroacetic anhydride, triflic anhydride, methanesulfonyl chloride and p-toluenesulfonyl chloride. This reaction is generally conducted in an appropriate solvent such as methylene chloride, chloroform, acetonitrile, acetone, THF or pyridine, with or without a base such as N,N-dimethylpyridine or a tri-(C_1-C_8 alkyl) amine, at temperature from about 0°C to about 120°C, preferably from about room temperature to about 80°C. Most preferably, an excess of acetic anhydride is used at a temperature between 80°C and the reflux temperature. The resulting compounds can then be heated in an appropriate solvent such as DMF, DMSO, sulfolane, dioxane, THF or NMP in the presence of base such as pyridine, a tri(C_1-C_4 alkyl) amine or sodium hydride, at temperature from about 0°C to about 180°C, preferably from about room temperature to about 150°C, to give the final cyclized compounds of formula I-Q.

Compounds of formula I-Q wherein B is -CN can be converted into the corresponding compounds wherein B is NR^1R^2 or $NHCR^1R^2R^{10}$ using a Curtius rearrangement reaction, as described below. Compounds of formula I-Q wherein B is CN are subjected to acid hydrolysis with, e.g, aqueous phosphoric acid, at a temperature between about 80°C and about 150°C, to yield the corresponding compounds wherein B is COOH. Compounds of the formula I-Q wherein B is COOH can be converted into the corresponding compounds wherein B is $-NH_2$ by reacting them with diphenylphosphorylazide in t-butyl alcohol in the presence of a tri(C_1-C_4 alkyl) amine, followed by acid hydrolysis using, e.g., trifluoroacetic acid, according to procedures well known in the art. The amino derivatives so formed can be converted, also using standard methods well known in the art, into the corresponding compounds wherein B is $NR^1R^2R^{10}$ via an alkylation or reduction amination reaction. Such a procedure is described above for forming compounds of the formula IB.

Reaction of compounds of formula I-Q wherein B is CN with a Grignard reagent (e.g., R^2MgX' wherein X' is halo) at a temperature from about 0°C to about room temperature in THF, ether or dioxane, followed by quenching with an acid, using the conditions well known in the art, will afford the corresponding ketones of formula I-Q wherein B is COR^2. Reduction of such ketones with sodium borohydride in a C_1-C_5 alkyl alcohol will afford the corresponding compounds of formula I-Q wherein B is CHR^2OH. Alkylation of compounds of formula I-Q wherein B is CHR^2OH with R^1-L (wherein L is a leaving group such as halo, mesylate or tosylate) in the presence of a base such as sodium hydride or potassium hydride will yield the corresponding compounds wherein B is CHR^1R^2. This reaction is typically carried in an appropriate solvent, e.g., THF, dioxane, ether, toluene or DMSO, at temperature between about 0°C and about 100°C, preferably between about 0°C and about room temperature.

The starting materials and intermediates of formulas IV, V, VI, VII, VIII, IX and X are commercially available, known in the art, or able to be synthesized using the procedures disclosed in PCT Patent Application PCT/IB95/00439, PCT Patent Application PCT/IB95/00373, U.S. Patent Application 08/481,413, U.S. Patent Application 08/448,539, and U. S. Patent Application 08/254,820, all of which are referred to and incorporated herein by reference in their entireties above.

In each of the above reactions, pressure is not critical. Pressures in the range of about 0.5-20 atm (0.5-20 bars) are suitable, and ambient pressure (generally, about one atmosphere) is preferred as a matter of convenience. Also, for those reactions where the preferred temperature varies with the particular compounds reacted, no preferred temperatur is stated. For such reactions, pref rred temperatur s for particular reactants may be d t rmin d by monitoring the r action using thin layer chromat graphy or gas chr matography/mass spectroscopy.

Th preparation of other compounds f the formula I not specifically described in th foregoing experimental section can b accomplished using combinations or variations of the reacti ns described above that will be apparent t those

skilled in the art.

Compounds of the formulas I, II and III that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acc ptabl for administration to animals, it is often desirable in practice to initially isolat a compound of th formulas I, II or III from the reaction mixture as a pharmac utically unacc ptable salt and th n simply convert the latt r back to the fr base compound by treatment with an alkaline reagent, and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of compounds of the formulas I, II and III can be prepared in a conventional manner by treating a solution or suspension of the corresponding free base with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques can be employed to isolate the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

Compounds of the formulas I, II and III that are also acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula I. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The active compounds of this invention may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of formulas I, II and III and their pharmaceutically acceptable carriers can then be readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, methylcellulose, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions containing an active compound of this invention or a pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosages for compounds of the formulas I, II or III and their salts will depend on the intended route of administration and factors such as the age and weight of the patient, as generally known to a physician. The dosages will also depend on the particular illness to be treated. For instance, the daily dosage for stress-induced illnesses, inflammatory disorders, Alzheimer's disease, gastro-intestinal diseases, anorexia nervosa, hemorrhagic stress and drug and alcohol withdrawal symptoms will generally range from about 0.1 to about 50 mg/kg body weight of the patient to be treated.

Methods that may be used to determine the CRF antagonist activity of the active compounds of this invention and their pharmaceutically acceptable salts are described in Endocrinology, 116, 1653-1659 (1985) and Peptides, 10, 179-188 (1985). The binding activities for compounds of f rmulas I, II and III, expressed as IC_{50} values, generally range from about 0.5 nanomolar to about 10 micromolar.

Th pr sent invention is illustrated by the following xamples. It will be understood, how ver, that th inv ntion is n t limit d to th specific details of thes examples. Melting points are uncorrected. Proton nuclear magn tic resonance

spectra (^{1}H NMR) and C^{13} nuclear magnetic resonance spectra (C^{13} NMR) were measured for solutions in deuterochloroform ($CDCl_3$) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

The following abbreviations are used in the Examples: Ph=phenyl; iPr=isopropyl; HRMS=high resolution mass spectrum.

EXAMPLE 1

2,5,6-Trimethyl7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3d]pyrimidine

To a solution of 2,4,6-trimethylphenol (111 mg, 0.82 mmol) in 3 ml of DMSO was added 60% sodium hydride (NaH) in oil (32 mg, 0.8 mmol). After stirring for 10 min, 4-chloro-2,5,6-trimethyl-7-(1-propylbutyl)-7H-pyrrolo[2,3,-d]pyrimidine (200 mg, 0.68 mmol) was added. The resulting mixture was heated at 135°C in an oil bath for 3 hours. An additional 10 mg of 60% NaH was added and the mixture was heated at 135°C for an additional 1 hour and cooled to room temperature. The mixture was quenched with water and extracted with ethyl acetate (EtOAc). The organic layer was washed with 2N sodium hydroxide (NaOH) and brine, and then dried and concentrated to give a brown oil. The oil was purified through silica gel column chromatography using chloroform ($CHCl_3$):hexane=4:1 as eluent to give the title compound (79%) as a light green oil. ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 2.33 (s, 6H), 2.12 (s, 6H), 1.7-1.9 (m, 3H), 0.95-1.35 (m, 6H), 0.88 (s, 6H) ppm. MS : [P+] = 393 (100%). The corresponding HCl salt was also prepared.

EXAMPLE 2

1-(1-Ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one

To a solution of N4-(1-ethylpropyl)-6-methyl-N2-(2,4,6-trimethylphenyl)-pyridine-2,3,4-triamine (250 mg, 0.77 mmol) in 5 ml of dry tetrahydrofuran (THF) was treated with triphosgene (89 mg, 0.3 mmol) and triethylamine (189 mg, 1.87 mmol) at 0°C and stirred at room temperature for 0.5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 260 mg of a tan solid. The residue was purified through silica gel column chromatography to give 200 mg of the title compound (> 90% pure) and 60 mg of white crystals of the title compound. Mp 148-150°C. ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 2H), 6.39 (s, 1H), 6.00 (s, 1H, NH), 5.94 (s, 1H, NH), 4.03 (m, 1H), 2.44 (s, 3H), 2.32 (s, 3H), 2.20 (s, 6H), 1.80-2.05 (m, 4H), 0.82 (t, 6H) ppm.

The following compounds were prepared by a method analogous to that described in Example 2 starting from the appropriate 4-substituted-N-(1-ethyl-propyl)-2-methyl-pyrimidine-5,6-diamineor2-substituted-N4(1-ethylpropyl)-6-methyl-pyridine-3,4-diamine and purified from silica gel column chromatography.

EXAMPLE 3

9-(1-Ethylpropyl)-2-methyl-6-(2,4,6-trimethylphenylamino)-7,9-dihydro-purin-8-one

^{1}H NMR ($CDCl_3$) δ 6.98 (s, 2H), 6.81 (s, 1H), 5.709 (brs, 1H), 4.14 (m, 1H), 2.44 (s, 3H), 2.33 (s, 3H), 2.20 (s, 6H), 2.0-2.3 (m, 2H), 1.8-2.0 (s, 3H), 0.81 (t, 6H) ppm.

EXAMPLE 4

1(1-Ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one

Mp 235-237°C. Anal. calc'd for $C_{21}H_{27}N_3O_2$ (C,H,N) **[Fill in date or Delete]**. ^{1}H NMR ($CDCl_3$) δ 7.02 (s, 1H), 6.91 (s, 2H), 6.61 (s, 1H), 4.12 (m, 1H), 2.39 (s, 3H), 2.32 (s, 3H), 2.12 (s, 6H), 1.8-2.1 (m, 4H), 0.87 (t, 6H) ppm.

EXAMPLE 5

1-(1-Ethyl propyl)-6-methyl-4-(2,4,6-trimethylphenoy)-1H-imidazo[4,5-c]pyridine

A mixture of N4-(1-ethylpropyl)-6-methyl-2-(2,4,6-trimethylphenoxy)-pyridine-3,4-diamine (160 mg, 0.49 mmol), trimethyl orthoformate (62 mg, 0.59 mmol) and paratosylalcohol (p-TsOH) (10 mg) in 20 ml of toluene was heated at reflux under a Dean-Stark trap apparatus for 24 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the title compound (160 mg, 97%) as a light brown oil.

The oil was purified through silica gel column chromatography using 2% methan l (MeOH) in chloroform as luent to giv a tan solid. Mp 127-131°C. ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H), 6.90 (s, 2H, 6.81) (s, 1H), 4.02 (m, 1H), 2.37 (s, 3H), 2.32 (s, 3H), 2.13 (s, 6H), 1.98 (m, 4H), 0.87 (t, 6H) ppm.

EXAMPLE 6

1-(1-Ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one

A solution of 1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one (100 mg, 0.28 mmol) in 5 ml of dry THF was treated with lithium bis(trimethylsilyl)amide (0.31 ml, 1M in THF, 0.31 mmol) at -78°C. After 20 min, the mixture was quenched with 1 ml of methyl iodide and stirred at room temperature for 1 hour. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 110 mg of an off-white solid which was recrystallized from isopropyl ether to give white crystals. Mp 152-154°C; ^{1}H NMR ($CDCl_3$) δ 6.91 (s, 2H), 6.57 (s, 1H), 4.18 (m, 1H), 3.73 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H), 2.12 (s, 6H), 1.9-2.1 (m, 2H), 1.7-1.9 (m, 2H), 0.88 (t, 6H) ppm.

EXAMPLE 7

1-(1-Ethypropyl)-3,6-dimethyl-4-(2,4,6-trimethyphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one

The title compound was prepared by a method analogous to that described in Example 6 starting from 1-(1-ethyl-propyl)-6-methyl-4-(2,4,6-trimethyphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one. ^{1}H NMR ($CDCl_3$) δ 6.91 (s, 2H), 6.42 (s, 1H), 5.77 (s, 1H), 4.13 (m, 1 H), 3.49 (s, 3H), 2.31 (s, 6H), 2.17 (s, 6H), 1.9-2.2 (m, 2H), 1.7-1.9 (m, 2H), 0.86 (t, 6H) ppm.

EXAMPLE 8

1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-[1,2,3]triazolo[4,5-c]pyridine

To a solution of 2-(2,4,6-trimethylphenoxy)-N4-(1-ethylpropyl)-6-methyl-pyridine-3,4-diamine (640 mg, 1.95 mmol) and 7 ml of 48% hydrobromic acid was added a solution of sodium nitrite (146 mg, 2.11 mmol) in 2 ml of water dropwise over 5 min at 0°C. The resulting mixture was treated with cuprous bromide Cu(I)Br (145 mg, 1.01 mmol) and then heated at reflux for 15 min. The mixture was cooled to room temperature and diluted with water, basified with ammonium hydroxide and extracted twice with ethyl acetate. The organic layer was dried and concentred to give 710 mg (93% yield) of the title compound as brown crystals, which was further recrystallized from isopropyl ether to give the title compound as golden crystals. ^{1}H NMR ($CDCl_3$) δ 6.92(s,2H), 6.84(s,1H), 4.5(m,1H), 2.40(s,3H), 2.32(s,3H), 2.13(s, 6H), 2.0-2.4(m,4HO, 0.83(t,6H)ppm.

EXAMPLE 9

7-Bromo-1-(1-ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-[1,2,3] triazolo[4,5-c]pyridine

A mixture of 2-(2,4,6-trimethylphenoxy)-N4-(1-ethylpropyl)-6-methyl-pyridine-3,4-diamine (250 mg, 0.763 mmol), n-butyl nitrite (118 mg, 1.15 mmol) and $CuBr_2$ (205 mg, 0.916 mmol) in anhydrous acetonitrile was heated at 65°C for 2 hours. The mixture was quenched with 16 ml of 2N HCl and extracted 3 times with ethyl acetate. The organic layer was dried and concentrated to give a light brown form (0.310 g). The crude material was purified through silica gel column chromatography using 1:1 chloroform:ethyl acetate as eluent to give 160 mg of 1-(1-ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-[1,2,3]triazolo [4,5-c]pyridine and 60 mg of 7-bromo-1-(1-ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-[1,2,3]triazolo [4,5-c]pyridine. Mp 154-156°C; ^{1}H NMR ($CDCl_3$) δ 6.92(s,2H), 5.5(m,1H), 2.51(s,3H), 2.33(s,3H), 2.13(s,6H), 2.2-2.45(m,2H), 2.0-2.2 (m,2H), 0.87(t,6H) ppm.

EXAMPLE 10

1-(1-Ethyl-propyl)-6,7-dimethyl-4-(2,4,6-trimethyl-phenoxy)-1H-[1,2,3] triazolo[4,5-c]pyridine

To a -78°C solution of 7-bromo-1-(1- thyl-propyl)-6-m thyl-4-(2,4,6-trimethyl-phenoxy)-1H-[1,2,3]triazolo[4,5-c] pyridine (33 mg, 0.079 mm l) in 2 ml of dry THF was added 2.5 M nBuLi in hexan (0.047 ml, 0.019 mmol) and stirred at that temperature for 5 min. An excess of MeI (0.5 ml) was added and the mixture was stirred at that temp rature for

15 min, then gradually warmed to room temperature for 1 hour. The mixtur was quenched with saturated ammonium chloride and extracted with ethyl acetate. Th organic lay r was dried and concentrated to give 31 mg of a gold n oil. The oil was purified through silica gel column chromatography using 5% ethyl acetate in hexane as eluent to give the title compound as white crystals. Mp 127.129°C; ^{1}H NMR ($CDCl_3$) δ 6.91 (s,2H), 4.83(m,1H), 2.51(s,3H), 2.38(s,3H), 2.33(s,3H), 2.13(s,6H), 2.3-2.5(m,2H), 1.9-2.2(m,2H), 0.86(t,6H) ppm.

EXAMPLE 11

1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxyl)-1,3-dihydro-pyrrolo[3.2-c]pyridin-2-one

A mixture of [4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-acetonitrile (800 mg, 2.27 mmol) , 6 ml of 85% phosphoric acid and 2 ml of water was heated at reflux for 2 hours and cooled to room temperature. The reaction mixture was neutralized with 2N NaOH and extracted twice with chloroform. The chloroform layer was dried and concentrated to give a yellow solid. The solid was purified through silica gel column chromatography using hexane to 6% ethyl acetate in hexane as eluent to give 730 mg (92.2%) of a white solid. ^{1}H NMR ($CDCl_3$) δ 6.87(s, 2H), 6.5(s,1H), 4.1(m,1H), 3.12(s,2H), 2.38(s,3H), 2.30(s,3H), 2.10(s,3H), 1.7-2.0(m,4H), 0.8(t,6H) ppm.

EXAMPLE 12

1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine

A mixture of 1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one (12 mg, 0.034 mmol) and 2M BH3-DMS complex in THF (0.1 ml, 0.2 mmol) in 1 ml of dry THF was heated at reflux for 3 hours. The mixture was quenched with dilute HCl and stirred for 1 hour, then neutralized, and extracted with ethyl acetate. The organic layer was dried and concentrated. The residue was purified through silica gel column chromatography using hexane to 4% ethyl acetate in hexane as eluent to give 6 mg of the title compound. ^{1}H NMR ($CDCl_3$) δ 6.88(s,2H), 6.84(s,1H), 6.74(s,1H), 5.97(s,1H), 4.00(m,1H), 2.43(s,3H), 2.30(s,3H), 2.10(s,6H), 1.7-1.9(m,4H), 0.75 (t,6H) ppm.

EXAMPLE 13

1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine

A mixture of 1-(1-Ethyl-propyl)-6-methyl-4--(2,4,6-trimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one (49 mg, 0.142 mmol) and 2M BH3-DMS complex in THF (0.5 ml, 1.0 mmol) in 1 ml of dry THF was heated at reflux for 3 hours. The mixture was quenched with dilute HC and stirred for 48 hours, then neutralized, and extracted with ethyl acetate. The organic layer was dried and concentrated. The residue was purified through silica gel column chromatography using hexane to 20% ethyl acetate in hexane as eluent to give 15 mg (31%) of the title compound as a clear oil and 18 mg (38%) of 1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine. ^{1}H NMR ($CDCl_3$) of the title compound: δ6.84(s,2H), 5.89(s,1H), 3.3(t,2H), 3.2(m,1H), 2.5(t,2H), 2.28(s,6H), 2.14(s,6H), 1.4-1.6 (m,4H), 0.88(t,6H)ppm.

EXAMPLE 14

1-(1-Ethyl-propyl)-6-methyl-4-(2y4y6-trimethyl-phenoxyl)-1H-imidazo[4,5-c]pyridin-2-ylamine

A mixture of of 2-(2,4,6-trimethylphenoxy)-N4-(1-ethylpropyl)-6-methyl-pyridine-3,4-diamine (200 mg, 0.611 mmol) and 5M BrCN in acetonitrile (0.12 ml, 0.611 mmol) in 3 ml of anhydrous acetonitrile was stirred at room temperature overnight. The mixture was quenched with water and saturated sodium bicarbonate and extracted 3 times with ethyl acetate. The organic extracts was washed with brine, dried and concentrated to give 240 mg of a light green form. The residue was purified through silica gel column chromatography using 10% methanol in chloroform as eluent to give 146 mg (68%) of the title compound as a tan solid. Mp 208-210°C. ^{1}H NMR ($CDCl_3$) δ 6.89 (s,2H), 6.68(s,1H), 5.03(s, 2H), 3.84(m,1H), 2.31(s,6H), 2.13(s,6H, 1.8-2.2(m,4H), 0.89(t,6H) ppm.

EXAMPLE 15

1-(1-Ethyl-propyl)-3,6-dimethyl-4-(2,4,6-trim thyl-ph noxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one

To a -78°C solution of 1-(1-ethyl-propyl)-6-methyl-4-(2,4,6-trim thylphenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one (352 mg, 1.0 mmol) in 2 ml of dry THF was added 2.5M BuLi in hexane (0.4 mmol, 1.0 mmol). The resulting mixture was stirred at -78°C for 30 min, then transferred to a -78°C solution of methyl iodide (3 ml) in 3ml of dry THF. The resulting mixture was stirred at -78°C for 1 hour, quenched with saturated ammonium chloride, extracted with ethyl acetate. The organic layer was dried and concentrated to give a clear oil which was purified through silica gel column chromatography using hexane to 10% ethyl acetate in hexane as eluent to give the title compound as tan solid 214 mg (68%). ^{1}H NMR ($CDCl_3$) δ 6.88 (s,2H), 6.47(s,1H), 4.1(m,1H), 3.56(q,1H), 2.30(s,3H), 2.26(s,3H), 2.07(s,6H), 1.7-2.0(m,4H), 1.60(d,3H), 0.86(t,6H) ppm.

EXAMPLE 16

1-(1-Ethyl-propyl)-3,3,6-trimethyl-4-(2,4,6-trimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one

The title compound was prepared by the method analogous to that described in the Example 15 starting from 1 equivalent of 1-(1-ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one and 2.5 equivalent of n-BuLi at -78°C, followed by quenching with excess of methyl iodide. ^{1}H NMR ($CDCl_3$) δ 6.88(s,2H), 6.46 (s,1H), 4.11(m,1H), 2.29(s,3H), 2.24(s,3H), 2.05(s,6H), 1.8-2.0(m,2H), 1.6-1.8(m,2H), 1.52(s,6H), 0.85(t,6H) ppm.

EXAMPLE 17

1-(1-Ethyl-propyl)-3,3,6-trimethyl-4-(2,4,6-trimethyl-phenoxy)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 1-(1-ethyl-propyl)-3,3,6-trimethyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one (50 mg) in 2 ml of dry THF was added excess of 2M borane-dimethyl sulfide complex in THF. The resulting mixture was heated at reflux for 6 hours. The mixture was quenched with dilute HCl and stirred for 30 min, neutralized with 2N NaOH, brine and extracted with ethyl acetate. The organic layer was dried and concentrated to givethe solid. The solid was purified through silica gel column chromatography using 10% ethyl acetate in chloroform as eluent to give the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 6.86(s,2H), 5.88(s,1H), 3.3(m,1H), 3.2(s,2H), 2.29(s,3H), 2.13(s,3H), 2.09(s,6H), 1.6(m,4H), 1.47(s,6H), 0.91(t,6H) ppm.

EXAMPLE 18

1-(1-Ethyl-propyl-3,6-dimethyl-4-(2,4,6-trimethyl-phenoxy)-1H-pyrrolo [3,2-c]pyridine

A mixture of 1-(1 ethyl-propyl)-3,6-dimethyl-4-(2,4,6-trimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one (20 mg, 0.0546 mmol) and 2M borane-dimethyl sulfide complex in THF (0.07 ml) in 1 ml of THF was heated at reflux for 2 hours. The mixture was quenched with dilute HCl and stirred for 30 min, then neutralized and extracted with ethyl acetate. The organic layer was dried and concentrated to give the crude residue. The residue was purified through silic gel column chromatography using hexane to 10% ethyl acetate in hexane as eluent to give the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 6.89(s,2H), 6.69(s,1H), 6.63(s,1H), 3.92(m,1H), 2.49(s,3H), 2.30(s,3H), 2.11(s,6H), 1.7-1.9(m,4H), 0.78(t,6H)ppm.

EXAMPLE 19

1-(1-Ethyl-propyl)-2-methoxy-3,6-dimethyl-4-(2,4,6-trimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine

To a 0°C solution of 1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one (134 mg, 0.381 mmol) in 2ml of HMPA was added 60% sodium hydride in oil (20 mg, 0.5 mmol) and the resulting mixture was stirred at 0°C for 10 min. Dimethyl sulfate (66.5 mg, 0.53 mmol) was added and stirred for 30 min. The reaction mixture was quenched with dilute acid to pH4 and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give a clear oil. The oil was purified through silica gel column chromatography using 3% ethyl acetate in hexane as luent to give 70 mg of th title compound as white solid. ^{1}H NMR ($CDCl_3$) δ 6.88 (s,2H), 6.61(s,1H), 4.0(m,1H), 3.95(s,3H), 2.44(s,3H), 2.29(s,3H), 2.26(s,3H), 2.10(s,6H), 1.95-2,1(m,2H), 1.7-1.9(m, 2H), 0.78(t,6H)ppm.

EXAMPLE 20

[1-(1-Ethyl-propyl)-6-methyl-1H-[1,2,3]triazolo[4,5-c]pyridin-4-yl]-(2,4,6-trim thyl-ph nyl)-amine

A mixtur of N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine (250 mg, 0.766 mmol) and butyl nitrite (119 mg, 1.15 mmol) in 16 ml of acetonitrile was heated at 65°C for 2 hours. The mixture was quenched with 2N HCl, then neutralized to pH 7 and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 250 mg of a golden brown residue. tlc indicated two components were obtained from this reaction, in which the more polar one is the title compound. The title compound was isolated as a white crystals, mp 140-142°C, after silica gel column chromatography using 10% ethyl acetate in hexane as eluent. ^{1}H NMR ($CDCl^3$) δ 6.94(s,2H), 6.49(s,1H), 4.40(m,1H), 2.38(s,3H), 2.31(s,3H), 2.23(s,6H), 2.05-2.2(m,2H), 1.9-2.05(m,2H), 0.80(t,6H) ppm.

EXAMPLE 21

4-(4-Bromo-2,6-dimethyl-phenoxy)-1-(1-ethyl-propyl)-6-methyl-1H-oxazolo[5-4-c]pyridin-2-one

To a 0°C solution of 4-(1-ethyl-propylamino)-6-methyl-2-(4-bromo-2,6-dimethyl-phenoxy)-pyridin-3-ol (40 mg, 0.101 mmol) was added triphosgene (10 mg, 0.035 mmol) and triethylamine (7 mg, 0.07 mmol) in 1 ml of dry THF. The resulting mixture was stirred overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated. The residue was purified through silica gel column chromatography to give 26 mg (61%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.22(s,2H), 6.60(s,1H), 4.02(m,1H), 2.31(s,3H), 2.12(s,6H), 1.8-2.2(m,4H), 0.94(t,6H)ppm.

EXAMPLE 22

1-(1-Ethyl-propyl)-6-methyl-4-(2,4,6-trimethyl-phenoxy)-1H-oxazolo[5,4-c]pyridin-2-one

The title compound was prepared as a grey solid by the method analogous to that described in the Example 21 starting from 4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ol and triphosgene. ^{1}H NMR ($CDCl_3$) δ6.87(s,2H), 6.55(s,1H), 3.98(m,1H), 2.29(s,3H), 2.28(s,3H), 2.09(s,6H), 1.9-2.05(m,2H), 1.8-1.9(m,2H), 0.90 (t,6H) ppm.

EXAMPLES 23(a) - 23(g)

The following compounds can be prepared by the method analogous to that described in Example 11 starting from [4-(1-ethyl-propylamino)-6-methyl-2-(substituted-phenoxy)-pyridin-3-yl]-acetonitrile and phosphoric acid.

(a) 1-(1-Ethyl-propyl)-6-methyl-4-(4-chloro-2,6-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(b) 1-(1-Ethyl-propyl)-6-methyl-4-(4-bromo-2,6-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(c) 1-(1-Ethyl-propyl)-6-methyl-4-(2-bromo-4-i-propyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(d) 1-(1-Ethyl-propyl)-6-methyl-4-(2,4-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(e) 1-(1-Ethyl-propyl)-6-methyl-4-(4-i-propyl-2,6-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(f) 1-(1-Ethyl-propyl)-6-methyl-4-(4-t-butyl-2,6-dimethyl-phenoxy)-1,3-dyhdro-pyrrolo[3,2-c]pyridin-2-one; and
(g) 1-(1-Ethyl-propyl)-6-methyl-4-(4-trifluoromethyl-2,6-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2c]-pyridin-2-one.

EXAMPLES 24(a) - 24(j)

The following compounds can be prepared by the method analogous to that described in Example 15 starting from 1-(1-Ethyl-propyl)-6-methyl-4-(substituted-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one and an appropriate base, such as BuLi, lithium diisopropylamide, r lithium bis(trimethylsilyl)amide, f llow d by quenching with an appropriate l ctrophile such as methyl iodide or thyl iodide.

(a) 1-(1-Ethyl-propyl-3,6-dimethyl-4-(4-chloro-2,6-dim thyl-phenoxy)-1,3-dihydro-pyrr lo[3,2-c]pyridin-

2-one;
(b) 1-(1-Ethyl-propyl)-3,6-dim thyl-4-(4-bromo-2,6-dim thyl-ph noxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-on ;
( ) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(2-bromo-4-i-propyl-ph noxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-on ;
(d) 1-(1-Ethyl-propyl)-3-ethyl-6-methyl-4-(4-chloro-2,6-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(e) 1-(Ethyl-propyl)-3-ethyl-6-methyl-4-(4-bromo-2,6-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(f) 1-(1-Ethyl-propyl)-3-ethyl-6-methyl-4-(2-bromo-4-i-propyl-phenoxy)-1.3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(g) 1-(1-Ethyl-propyl-3,6-dimethyl-4-(2,4-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(h) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-i-propyl-2,6-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
(I) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-t-butyl-2,6-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one; and
(j) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-trifluoromethyl-2,6-dimethyl-phenoxy)-1,3-dihydro-pyrrolo[3,2c] pyridin-2-one.

EXAMPLES 25(a) - 25(k)

The following compounds can be prepared by the method analogous to that described in Example 18 starting from 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(substituted-phenoxy)-1,3-dihydro-pyrrolo-[3,2-c]pyridin-2-one.

(a) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-chloro-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(b) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-bromo-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(c) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(2-bromo-4-i-propyl-phenoxy-1H-pyrrolo[3,2-c]pyridine;
(d) 1-(1-Ethyl-propyl)-3-ethyl-6-methyl-4-(4-chloro-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(e) 1-(1-Ethyl-propyl)-3-ethyl-6-methyl-4-(4-bromo-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(f) 1-(1-Ethyl-propyl)-3-ethyl-6-methyl-4-(2-bromo-4-i-propyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(g) 1-(1-Ethyl-propyl-3,6-dimethyl-4-(2-bromo-4-i-propyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(h) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(2-bromo-4-i-propyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(I) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-i-propyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(j) 1-(1-Ethyl-propyl-3,6-dimethyl-4-(4-t-butyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine; and
(k) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-trifluoromethyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine,

EXAMPLES 26(a) - 26(g)

(a) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-ethyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine

To a solution of 2.5 N n-BuLi in hexane in dry THF was added a solution of leq. of 1-(1-ethyl-propyl)-3,6-dimethyl-4-(4-bromo-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine in dry THF at -78°C. After stirring at that temperature for 5 min, an appropriate electrophile (e.g., DMF, formaldehyde, or a C_3-C_4 iodide) was added and the resulting mixture was stirred at -78°C for 30 min, then at 0°C for 15 min. The mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried and concentrated to give the title compound after silica gel column chromatography.

The following compounds can also be prepared using the foregoing procedure:

(b) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-propyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]-pyridine;
(c) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-hydroxymethyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(d) 1-(1-Ethyl-propyl)-3,6-dimethyl-4-(4-formyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(e) 1-(1-Ethyl-propyl)-3-ethyl-6-methyl-4-(4-propyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine;
(f) 1-(1-Ethyl-propyl)-3-ethyl-6-methyl-4-(4-hydroxymethyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine; and
(g) 1-(1-Ethyl-propyl)-3-ethyl-6-methyl-4-(4-formyl-2,6-dimethyl-phenoxy)-1H-pyrrolo[3,2-c]pyridine.

EXAMPLES 27(a) - 27(f)

The following xamples can be pr pared by a reaction sequence similar to thos described in Examples 11, 15 and 18 (sequentially), starting from [4-(1-hydroxymethylpropylamin)-6-m thyl-2-(substitut d-ph noxy)-pyridin-3-yl]-

acetonitrile.

(a) 2-[4-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl]-butan-1-ol;
(b) 2-[4-(4-bromo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl]-butan-1-ol;
(c) 2-[4-(4-I-propyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrr lo[3,2-c]pyridin-1-yl]-butan-1-ol;
(d) 2-[4-(4-Ethyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl-butan-1-ol;
(e) 2-[4-(4-trifluoromethyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl]-butan-1-ol; and
(f) 2-[4-(2-bromo-4-i-propyl-phenoxy)-3,6-dimethyl-pyrrolo[3,2-c]pyridin-1-yl]-butan-ol.

PREPARATION A

2,5,6-Trimethyl-7-(1-propylbutyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol

A mixture of N-[3-cyano-4,5-dimethyl-1-(1-propylbutyl)-1H-pyrrol-2-yl]-acetamide (2.16 g, 7.8 mmol) and 85% phosphoric acid (3.5 ml) was heated at 150°C for 1 hour. The mixture was quenched with water and extracted with chloroform. The organic layer was dried and concentrated to give the title compound as white solid, ^{1}H NMR ($CDCl_3$) δ 12.4 (brs, 1H), 4.7 (brs) and 4.0 (brs, total of 1H), 2.46 (s, 3H), 2.36 (s, 3H), 1.6-2.4 (m, 7H), 1.74 (m, 2H), 0.9-1.4 (m, 4H), 0.85 (t, 6H) ppm.

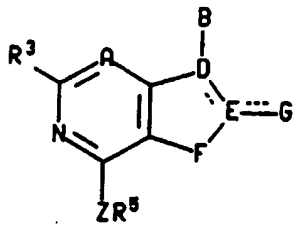
PREPARATION B

4-Chloro-2,5,6-trimethyl-7-(1-propylbutyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of 2,5,6-trimethyl-7-(1-propylbutyl)-7H-pyrrolo[2,3,-d]pyrimidin-4-ol (524 mg, 0.19 mmol) and phosphorous oxychloride (5.5 ml) was heated at reflux overnight. The mixture was cooled and poured into ice and extracted with ethyl acetate. The organic layer was neutralized with sat. sodium carbonate and brine, dried and concentrated to give the title compound as green solid (96%) which was purified through silica gel column chromatography using 1:1 hexane:chloroform as eluent to give the title compound as white crystals. ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3H), 2.38 (s, 6H), 2.32 (brs, 3H), 1.65-1.9 (m, 3H), 0.8-1.35 (m, 6H), 0.84 (t, 6H) ppm.

Claims

1. A compound of the formula



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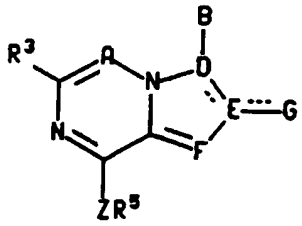
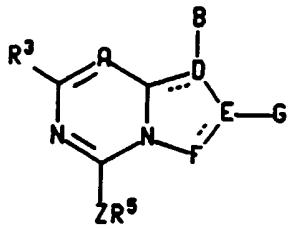


II

or



III

or a pharmaceutically acceptable salt thereof, wherein
the dashed lines represent optional double bonds;

A is nitrogen or CR^7;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is either double bonded to E in formulas I and II or double bonded to the adjacent carbon atom common to both fused rings in formula III, or D is CH and is single bonded to E in formulas I and II;

E is nitrogen, CH or carbon;

F is oxygen, sulfur, CHR^4 or NR^4 when it is single bonded to E and F is nitrogen or CR^4 when it is double bonded to E;

G, when single bonded to E, is hydrogen, C_1-C_4 alkyl, $-S(C_1$-C_4 alkyl), $-O(C_1$-C_4 alkyl), NH_2, $-NH(C_1$-C_4 alkyl) or $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), wherein each of the C_1-C_4 alkyl groups of G may optionally be substituted with one hydroxy, $-O(C_1$-C_2 alkyl) or fluoro group; G, when double bonded to E, is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D or F, is absent;

R^1 is hydrogen, C_1-C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, $-C(=C)O-(C_1$-$C_4)$alkyl, $-OC(=O)(C_1$-C_4 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-NHCO(C_1$-C_4 alkyl), -COOH, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 al)(C_1-C_2 alkyl), $-S(C_1$-C_4 alkyl), -CN, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), wherein each of the C_1-C_4 alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or (C_1-C_4 alkylene) aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, $-OC(=O)(C_1$-C_6 alkyl), $-OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_6 alkyl), amino, $-NH(C_1$-C_2 alkyl), $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), $-N(C_1$-C_4 alkyl)-CO-(C_1-C_4 alkyl), $-NHCO(C_1$-C_4 alkyl), -COOH, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), -SH, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl) and $-SO_2NH(C_1$-C_4 alkyl)(C_1-C_2 alkyl);

$-NR^1R^2$ or $CR^1R^2R^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R^3 is hydrogen, C_1-C_4 alkyl, $-O(C_1$-C_4 alkyl), chloro, fluoro, bromo, iodo, -CN, $-S(C_1$-C_4 alkyl) or $-SO_2(C_1$-C_4 alkyl) wherein each of the (C_1-C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substituted with one substituent R^9 selected from hydroxy, fluoro and (C_1-C_2 alkoxy);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4)alkyl, -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl), wherein each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoing R^4 groups may optionally contain one or two double or triple bonds and may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH_3, fluoro, chloro, C_1-C_3 thioalkyl, -CN, -COOH, -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl) and -NO_2;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein Z^4 is hydrogen, C_1-C_4 alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{12} wherein one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, -CF_3, -NO_2, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyo(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, C_1-C_4 alkyl, halo, cyano, hydroxy, -O(C_1-C_4 alkyl) -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4alkyl), -OCF_3, -CF_3, -CH_2OH, -CH_2O(C_1-C_4 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), -NC(=O)(C_1-C_2 alkyl), NC(=O)O(C_1-C_2alkyl) or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14}can be cyano;

with the proviso that: (a) in the five membered rings of structures I, II and III, there can not be two double bonds adjacent to each other; and (b) when R^4 is attached to nitrogen, it is not halo, cyano or nitro;

or a pharmaceutically acceptable salt of such compound.

2. A compound according to claim 1 wherein: R^1 is C_1-C_6 alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3, or C_1-C_4 alkoxy group and may optionally contain one double or triple bond; and R^2 is benzyl, C_1-C_6 alkyl, which may optionally contain one double or triple bond, wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl may optionally be substituted with one fluoro, CF_3, C_1-C_2 alkyl, C_1-C_2 alkoxy or chloro group.

3. A compound according to claim 1 wherein: R^3 is methyl, ethyl, chloro or methoxy; R^4 is methyl, ethyl or trifluoromethyl; G is hydrogen, methyl, ethyl, or E=G is C=O, C=S; R^5 is phenyl, pyridyl, pyrimidyl which is substituted with more than two substituents independently selected from C_1-C_4 alkyl, -O(C_1-C_4 alkyl), (C_1-C_4 alkyl)-O-(C_1-C_4 alkyl), CF_3, OCF_3, -CHO, (C_1-C_4 alkyl)-OH, CN, Cl, F, Br, I and NO_2, wherein each of the foregoing (C_1-C_4) alkyl groups may optionally contain one double or triple bond.

4. A compound according to claim 1 wherein A is N, CH or CCH_3 which may optionally be substituted by fluoro, chloro, CF_3, C_1-C_4 alkyl or C_1-C_4 alkoxy.

5. A compound according to claim 1 having the formula I.

6. A compound according to claim 1 having the formula II.

7. A compound according to claim 1 having the formula III.

8. A compound according to claim 1 wherein F is NR^4.

9. A compound according to claim 1 wherein F is CHR^4.

10. A compound according to claim 1 wherein F is nitrogen and is double bonded to E.

11. A compound according to claim 1 wherein F is sulfur.

12. A compound according to claim 1 wher in E is carbon.

13. A compound according to claim 1 wherein E is nitrogen.

14. A compound according t claim 1 wher in E is NR^{25} and R^{25} is hydrogen, C_1-C_4 alkyl or $-CF_3$.

15. A compound according to claim 1 that is selected from:

2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
9-(1-ethylpropyl)-2-methyl-6-(2,4,6-trimethylphenylamino)-7,9-dihydro-purin-8-one;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-imidazo[4,5-c]pyridine;
1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one; and
1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one.

16. A pharmaceutical composition comprising a compound or salt thereof as claimed in any preceding claim, and a pharmaceutically acceptable diluent or carrier.

17. A compound or salt as claimed in any of claims 1 to 15, or a composition thereof as claimed in claim 16, for use as a medicament.

18. The use of a compound or salt as claimed in any of claims 1 to 15, or of a composition as claimed in claim 16, for the manufacture of a medicament for the treatment of (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; hypertension; tachycardia; congestive heart failure; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal disorders; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; ulcers; immune dysfunctions including stress induced immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; psychosocial dwarfism; and hypoglycemia in a mammal.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 8892

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	WO 94 13677 A (PFIZER) * page 17; claim 1 *	1-18	C07D487/04 A61K31/52 C07D471/04 C07D473/34 C07D498/04 //(C07D487/04, 239:00,209:00)
X	WO 94 13676 A (PFIZER) * page 15; claim 1 *	1-18	
X	US 4 725 601 A (UEDA ET AL.) * column 1 *	1-18	
X	EP 0 157 637 A (THE WELLCOME FOUNDATION) * claim 1 *	1-18	
X	US 4 904 666 A (FRIEBE ET AL.) * claim 1 *	1-18	
X	US 5 028 605 A (SABLAYROLLES ET AL.) * claim 1 *	1-18	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	19 February 1997	Lauro, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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& : member of the same patent family, corresponding document

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(54) **Anti-leukemic beta-glycosyl C-nucleosides.**

(30) Priority: **31.07.81 US 288848**

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(56) References cited:

TETRAHEDRON LETTERS, vol. 21, 1980, Pergamon Press Ltd., GB, pages 1013-1016, MU-III LIM et al.: "Synthesis of the Pyrrolo (3,2-d) Pyrimidine C-Nucleoside Isostere of Inosine1"

TETRAHEDRON LETTERS, vol. 22, 1981, Pergamon Press Ltd., GB, pages 25-28, MU-III LIM et al.: "Synthesis of "9-Deazaadenosine"; A new Cytotoxic C-Nucleoside Isostere of Adenosine"

The file contains technical information submitted after the application was filed and not included in this specification

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Description

This invention relates to beta-glycosyl C-Nucleoside compounds which are able to inhibit the growth of leukemic cells, according to the species defined in claim 1.

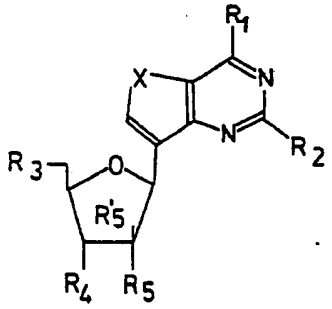
Methods f r making N-Nucleosides similar to the C-Nucleosides, which are the subject of this invention, are well known and well practiced. These techniques basically involve fusing an appropriate sugar to an appropriate base to form the required compound. These techniques cannot be applied to C-Nucleosides because of the low reactivity of the carbon site when compared with the nitrogen site.

To form C-Nucleosides, it has been found convenient to start with an appropriately substituted sugar moiety and "build" the desired base. However, known schemes for accomplishing this are difficult to follow and have only limited applicability because of the reagents used (see for example Gupta et al Abstract No. 40, 175 A. C. S. National meeting, Anaheim, California, March 13-17, 1978). Another procedure was also applied to the synthesis of 9-deazainosine in Lim et al., Tetrahedron Letters, Vol. 21, pp. 1013-1016 (1980). However, this compound has been found to have essentially no antitumor activity. For comparison, this compound is included in Table 1 of the patent description showing relative inhibition activity for various inventive compounds (X=NH, R_1=OH). A similar procedure was applied to synthesise 9-deazainosine according to Lim and Klein, Tetrahedron Letters, Vol. 22, pp. 25-28 (1981). This compound shows activity many orders of magnitude greater than 9-deazainosine as evidenced in Table 1.

It is the object of the invention to supply further potent new beta-glycosyl C-nucleoside compounds which exhibit activity against leukemia.

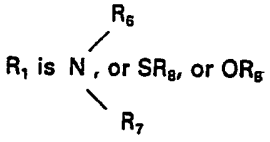
This object is solved by beta-glycosyl C-nucleoside compounds of the following formula:

Beta-glycosyl C-Nucleoside compounds of the formula



wherein

X is S or O



wherein R_6, R_7 and R_8 are independently selected from H or alkyl of 1 to 6 carbon atoms; or

R_2 is H,

R_3 is OH,

R_4 is OH,

R_5 is OH or H,

R'_5 is H.

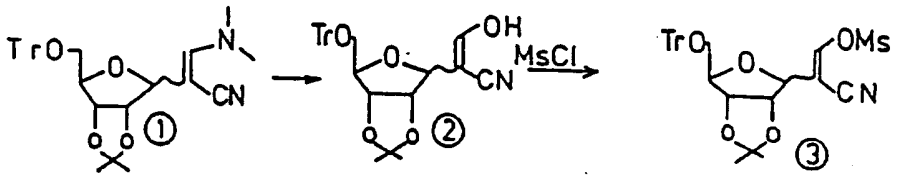
Further subclaims 2—5 refer to especially useful compounds.

The beta-glycosyl C-nucleoside compounds of the present invention have been shown to have anti-leukemic activity using usual techniques of the art. The results of these tests were summarized in Table 1. In addition, *in vivo* antitumor activity has been shown as summarized in Table 2. It is noted that the first compound in Table 1 is the compound reported in Lim et al (supra). This compound shows a lack of activity. Similar tests were also run on certain alpha-glycosyl nucleosides analogous to the inventive beta-glycosyl compounds, however these were found to be without activity.

The following preparative examples illustrate the presently preferred method of synthesizing the compounds of the present invention. (By lower alkyls is meant straight or branched alkyls of up to 6 carbon atoms.)

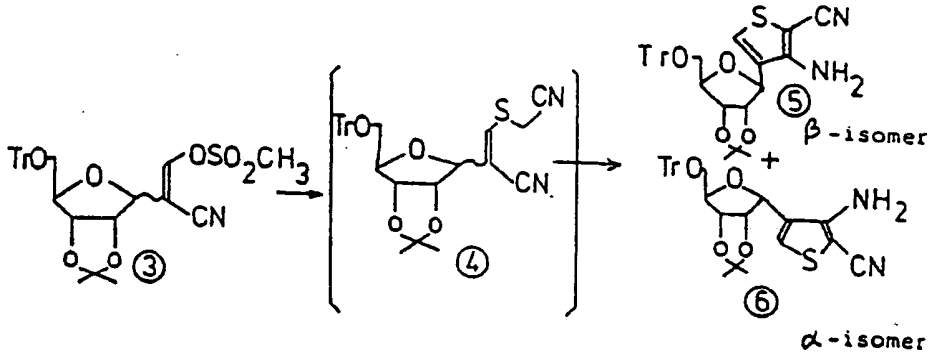
The invention therefor relates also to a method as claimed in claim 6

Preparative Example for Thieno (3,2-d)-(and Furo (3,2-d)) Pyrimidine Adenosine Analogs



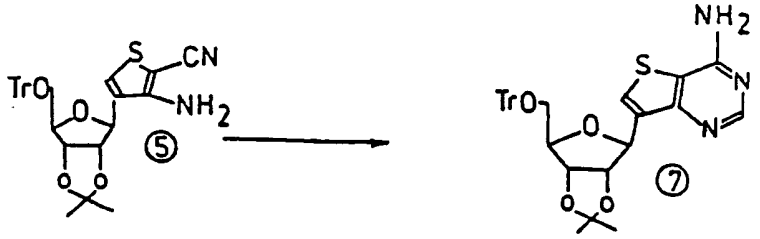
3-Methanesulfonyloxy-2-(2'3'-0-isopropylidene-5'-0-trityl-D-ribofuranosyl)-acrylonitrile

Hydrolysis of 24 g (47 mmol) of dimethylamino acrylonitrile ① as described previously afforded the corresponding crude 2-formyl acetonitrile derivative ②. Without purification ② was dissolved in 160 ml of chloroform containing 8.30 ml of triethylamine and treated dropwise with a solution of 4.22 ml (54 mmol) of methanesulfonyl chloride in 160 ml of chloroform at 0°C with efficient stirring. After one hour at 0°C the reaction mixture was diluted to 500 ml with chloroform and washed well with brine. The organic layer was dried over sodium sulfate and evaporated to dryness to give a crude anomeric mixture of ③ obtained as a foam (22 g). Purification and separation by chromatography of a small sample afforded pure anomers which were readily identified by NMR spectroscopy. The crude material was of satisfactor purity to be utilized directly in the following step.



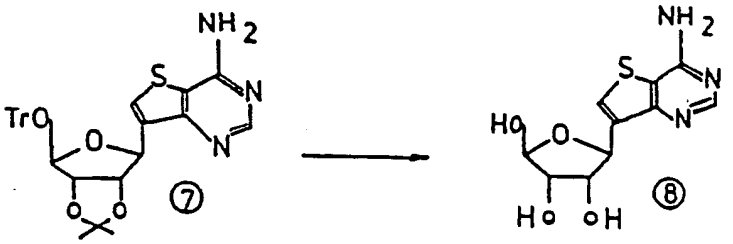
4-(2',3'-O-Isopropylidene-5'-O-trityl-β-(and α-) D-ribofuranosyl)-3-amino-2-cyanothiophene ⑤ and ⑥

To a solution of intermediate ③ (20 g, obtained from the previous step) in 430 ml of absolute ethanol was added acetylthioacetonitrile (8 g, 70 mmole). The reaction mixture was heated to reflux under N_2 for 7 hours and evaporated to dryness *in vacuo*. The residue was partitioned between chloroform and water (300 ml each) and the organic layer washed again with water. The chloroform solution was then dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The residue containing the α-β-anomeric mixture of ⑤ and ⑥ was purified by column chromatography on silica gel (Toluene) to give 5.6 g (24.5% from ① in the previous step) of the 3-amino-2-cyanothiophene β-C-nucleoside ⑤ and 2.5 g (11% from ①) of the corresponding α-C-nucleoside ⑥. Both were obtained as syrup. Their structure was confirmed by elemental analysis and NMR spectroscopy.



7-(2',3'-0-Isopropylidene-5'-0-trityl-β-D-ribofuranosyl)-4-amino-thieno(3,2-d)pyrimidine ⑦.

A solution of ⑤ (1.2 g, 2.2 mmol) in 30 ml of absolute ethanol was heated to reflux and to this was added in several portions 7 g of formamidine acetate (67 mmol) over a period of 7 days. The solvent was then removed *in vacuo* and the residue extracted with chloroform. The chloroform solution was then washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The crude material containing ⑦ was purified by column chromatography on silica gel (chloroform-methanol: 20/1) to give the blocked thien (3, 3-*d*) pyrimidine ⑦ (1.01 g, 80% from ⑤) as a foam. The structure was confirmed by elemental analysis and NMR spectroscopy.



7-(β-D-ribofuranosyl-4-amino-thieno(3,2-d)pyrimidine ⑧ (claim 2)

A mixture of the blocked C-nucleoside ⑦ (200 mg, 0.35 mmol) and 4 ml of a 12% solution of hydrogen chloride in methanol was stirred at room temperature for 10 minutes. Diethylether (15 ml) was then gradually added to precipitate ⑧ as an amorphous solid which slowly crystallizes. Filtration and washing with diethylether finally affords 98 mg (85%) of ⑧ as a dihydrochloride salt m.p. 154-155°C.

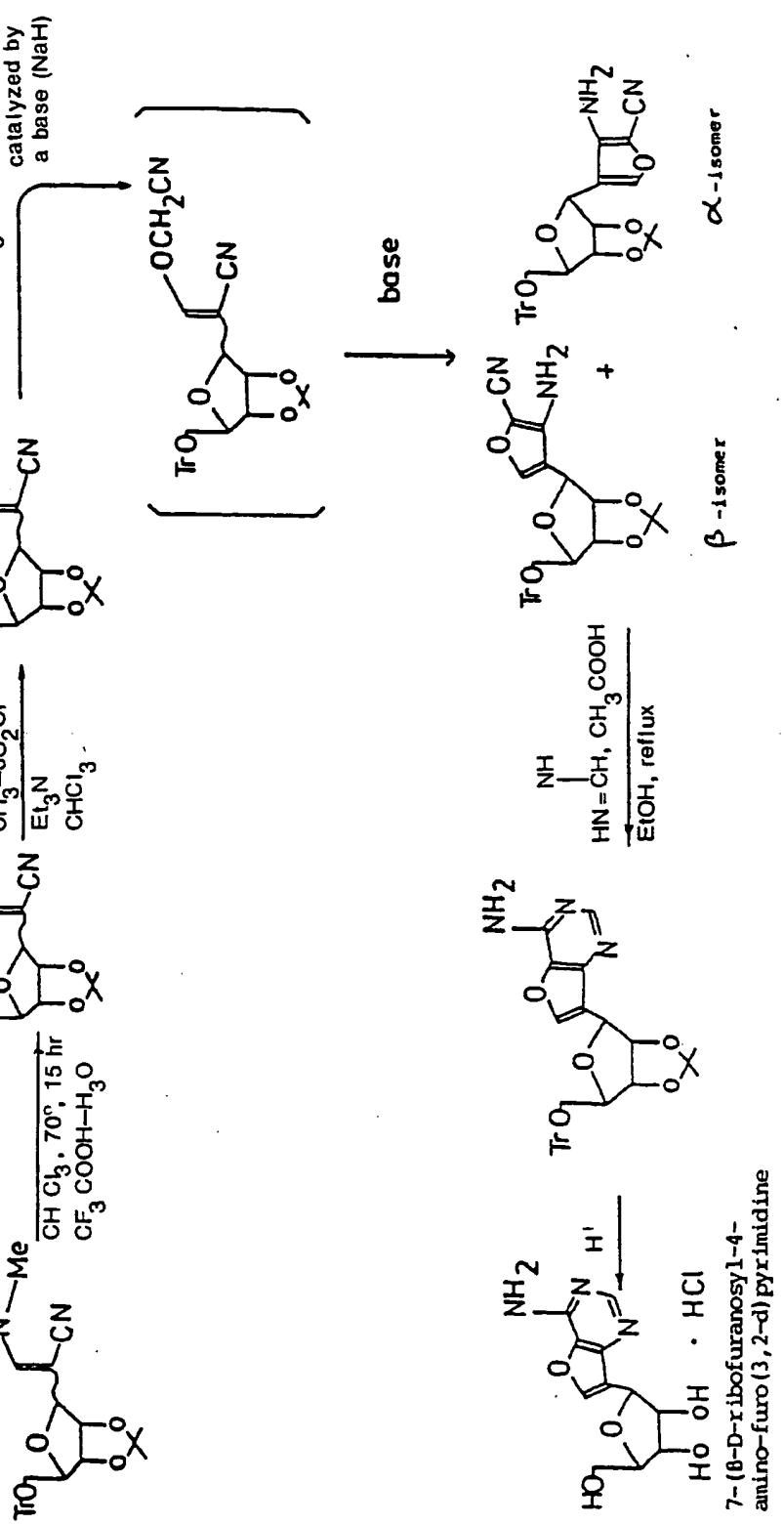
Elemental Analysis Calculated for: C: 37.08; H: 4.24; N: 11.79; S: 8.99; Cl: 19.90.

Found: C: 37.74; H: 4.17; N: 11.89; S: 9.30; Cl: 20.40.

The structure was also confirmed by NMR spectroscopy.

The furo (3,2-*d*) pyrimidine compounds are prepared in an analogous manner, as shown by the following reaction scheme when compared with this preparative example.

SEQUENCE FOR THE FURO [3, 2 d] PYRIMIDINE ADENOSINE ANALOG

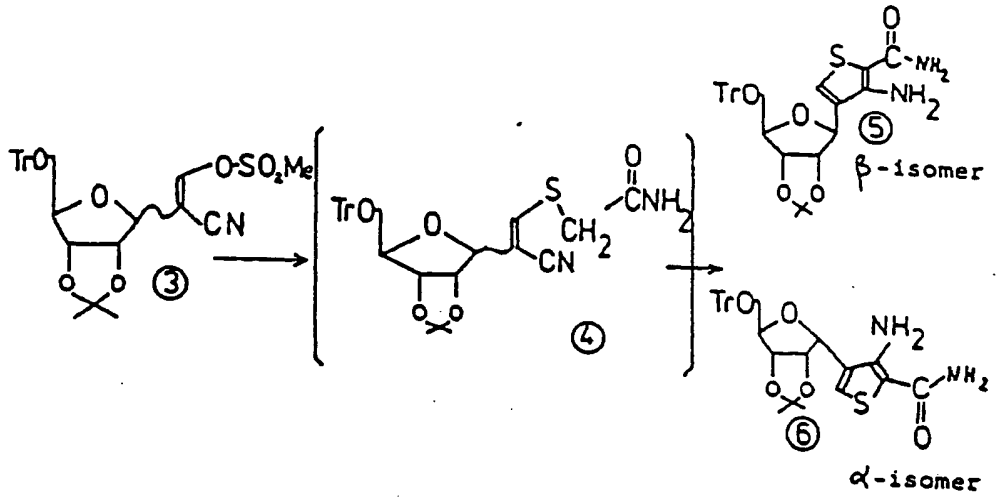


By utilization of the general procedure (J. Am. Chem. Soc., 1981 (103 pp 932-933)) for conversion of ribonucleosides to 2'-deoxynucleosides the following

7-(2'-Deoxy-β-D-ribofuranosyl)-4-amino-thieno(3,2-d)pyrimidine (claim 3)

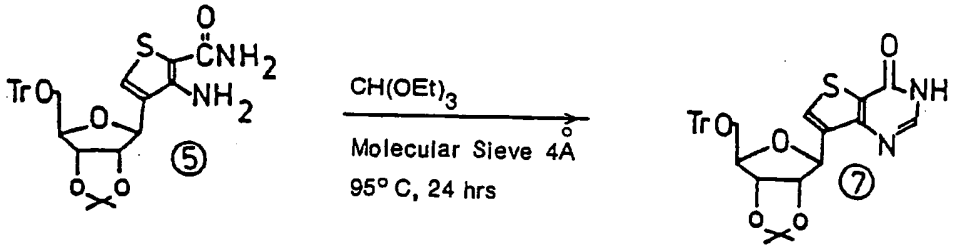
7-(2'-Deoxy-β-D-ribofuranosyl)-4-amino-furo(3,2-d)pyrimidine (claim 5)

Preparation of thieno (3,2-d) pyrimidine C-nucleoside derivatives



4-(2',3'-0-Isopropylidene-5'-0-trityl-β-(and -) D-ribofuranosyl)-3-amino-2-carboxamido-thiophene ⑤ and ⑥.

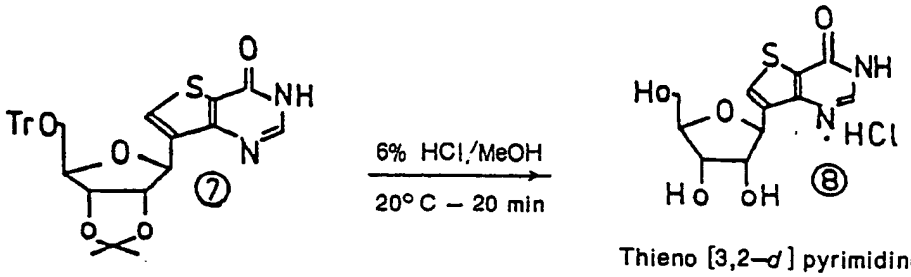
To a suspension of 3-mesyloxy acetonitrile ③ (6 g, 10.7 mmol, prepared by the method above described) in 180 ml of absolute ethanol was added mercaptocetamide (1.5 g, 16.4 mmol) and anhydrous sodium carbonate (1.7 g, 16.03 mmol). The reaction mixture was heated to reflux with stirring for 18 hours under a nitrogen atmosphere, allowed to cool to room temperature and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue containing the isomers ⑤ and ⑥ chromatographed on a column of silica gel with toluene-ethyl acetate (20:1). This separation afforded pure 3-amino-2-carboxamido-β-isomer ⑤ as a foam (2.62 g, 40% from ③ and the pure α-isomer ⑥ also a foam (2.94 g, 45% from ③). The structure of each was confirmed by elemental analysis and NMR spectroscopy.



7-(2',3'-0-Isopropylidene-5'-0-trityl-β-D-ribofuranosyl)-3H-4-oxo-thieno(3,2-d)-pyrimidine ⑦

To a suspension of 3-amino-2-carboxamido-thiophene ⑤ (3.5 g, 6.29 mmol) in 20 ml of triethylorthoformate was added 1 g of finely ground molecular sieve (4Å). The reaction mixture was heated at 95°C and stirred for 24 hours. After cooling to room temperature, it was filtered and to the clear filtrate was added 10 ml of petroleum ether (40-60°C) to precipitate compound ⑦ as a solid. This was collected by filtration, pressed into a cake, washed with petroleum ether and dried *in vacuo*. This procedure afforded ⑦ (2 g, 56%) as a white powder, mp 128-130°C.

The structure was confirmed by elemental analysis and by NMR spectroscopy.

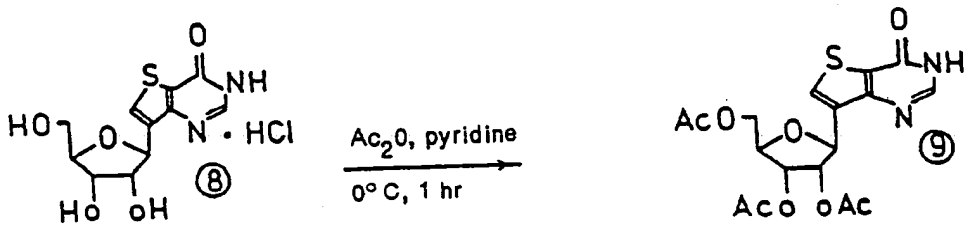


Thieno [3,2–*d*] pyrimidine analog of INOSINE

7-(β-D-Ribofuranosyl)-3H-4-oxo-thieno(3,2-d)pyrimidine monohydrochloride ⑧

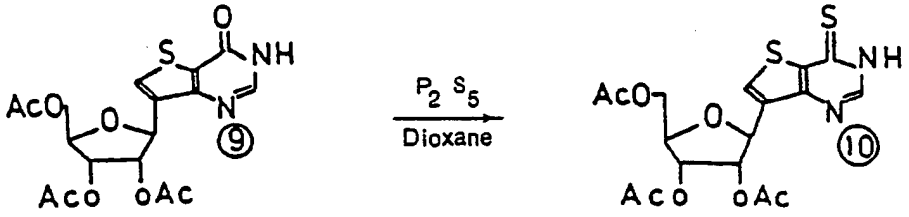
A mixture of compound ⑦ (5.8 g, 10.24 mmol) in 50 ml of a 6% solution of hydrogen chloride in methanol was stirred at 20°C for 20 minutes and 120 ml of diethyl ether was then added to gradually form a white precipitate. After one hour, the crystalline C-nucleoside monohydrochloride ⑧ was filtered and washed with ether to give 2.56 g (88%) of the desired product, mp 211-214°C.

Anal. Calcd: C: 41.19, H: 4.08, N: 8.73, S: 9.99
Found: C: 41.59, H: 4.10, N: 8.65, S: 9.85
Structure was confirmed by NMR spectroscopy



7-(2',3',5'-tri-0-acetyl-β-D-ribofuranosyl)-3H-4-oxo-thieno(3,2-d)pyrimidine ⑨

To a solution of compound ⑧ (1.5 g, 5.28 mmol) in anhydrous pyridine (5 ml) was added acetic anhydride (5 ml) at 0°C. After one hour the mixture was partitioned between chloroform (100 ml) and water (100 ml). The organic layer was washed with water (100 ml), dried over anhydrous Na_2SO_4 and evaporated to dryness *in vacuo*. The residue containing ⑨ was purified by chromatography on a silica gel column with chloroform-methanol (40:1) to give 1.61 g (75%) of the triacetate ⑨ as a colorless syrup. The structure was confirmed by elemental analysis and NMR spectroscopy.

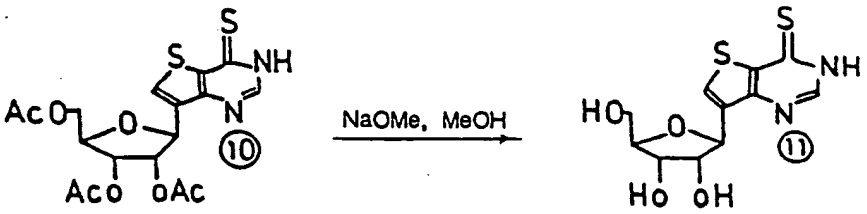


Thieno [3,2–*d*] pyrimidine analog of Thioniosine

7-(2',3',5'-Tri-0-acetyl-β-D-ribofuranosyl)-3H-4-thiono-thieno(3,2-d)pyrimidine ⑩

To a solution of ⑨ (3 g, 7.31 mmol) in 40 ml of dry dioxane heated to reflux was added 3 g of phosphorous pentasulfide in portions (200 mg each) over a period of 1.5 hours. Heating was continued until thin layer chromatography (chloroform/methanol: 10/1) indicated that the r action was completed. The solvent was removed *in vacuo* and the residue containing ⑩ was purified by chromatography on a column of silica gel (chloroform/methanol: 20/1) to give the thieno-pyrimidin thione ⑩ in pure f rm (2.62 g, 84%) as a foam.

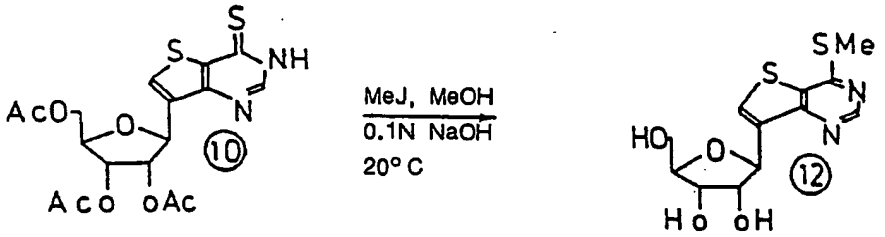
The structure was confirmed by NMR spectroscopy.



7-(β-D-ribofuranosyl)-3H-4-thiono-thieno(3,2-d)pyrimidine (11)

A solution of triacetate (10) (2.02 g, 4.74 mmol) in 40 ml of 0.1 N sodium methoxide in methanol was stirred at 20°C for 1 hour. The final solution was neutralized with IRC—50 (H+) ion exchange resin, filtered, and the filtrate evaporated to dryness *in vacuo.* The residue was dissolved in water and the aqueous solution washed with chloroform. The aqueous layer was lyophilized to give 1.36 g (95%) of pure 7-(β-D-ribofuranosyl)-3H-4-thiono-thieno(3,2-d)pyrimidine (11) as a powder.

The structure was confirmed by NMR spectroscopy



Thieno 3,2–*d* pyrimidine analog of Methylthio purine riboside

7-(β-D-Ribofuranosyl)-4-methylthio-thieno(3,2-d)pyrimidine (12)

To a solution of triacetate (10) (350 mg, 0.82 mmol) in a mixture of 3 ml of methanol and 3.3 ml of methyl iodide was added 10 ml of 0.1 N aqueous sodium hydroxide and the reaction mixture was stirred at room temperature for one hour. During this period, the product desired (12) precipitated. This was collected by filtration, washed with methanol then chloroform to afford 255 mg (98%) of 7-(β-D-ribofuranosyl)-4-methylthio-thieno(3,2-d)pyrimidine (12) as a crystalline (white needles) material. One recrystallization from boiling methanol afforded the analytical sample.

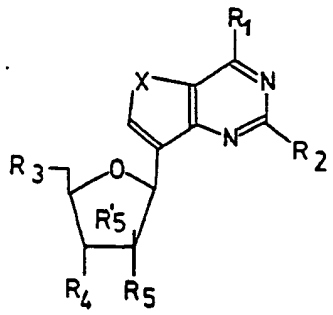
mp 226-228°C,

Anal Calcd: C: 45.84, H: 4.48, N: 8.90, S:20.39
Found: C: 45.89, H: 4.51, N: 8.88, S: 20.25

The structure was confirmed by NMR spectroscopy.

TABLE 1

In vitro activity (ID_{50}'s in µg/ml) f C-nucl osides in mouse and human leuk mic cell lines



		P—815	L—1210	RAJI	ALL—CCRF—CEM	HL—60
X=NH R_2=H R_3=R_4= R_5=OH, R_5'=H	R_1=OH, R_2=H	>10(0%)	>100	>100	>100	>100
	R_1=SH, R_2=H	5;6	—	—	—	—
	R_1=SMe, R_2=H	0.3	—	—	—	—
	R_1=NH_2, R_2=H	0.001	0.0008	0.002	0.0008	0.0003
X=S R_2=H R_3=R_4= R_5=OH, R_5'=H	R_1=OH, R_2=H	2.5	3.3	4.2	0.9	0.4
	R_1=SH, R_2=H	0.5	0.6	0.9	1.6	0.4
	R_1=SMe, R_2=H	0.03	0.07	0.03	0.006	0.008
	R_1=NH_2, R_2=H	0.0003	0.0006	0.002	0.0005	0.0005

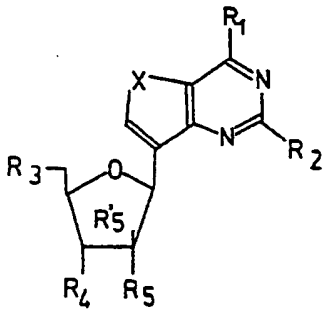


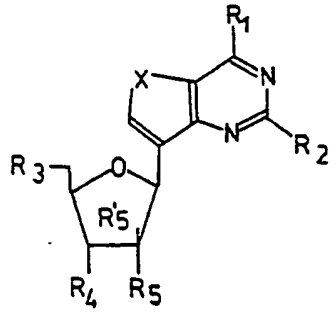
TABLE 2

In vivo activity of C-nucleosides in mice

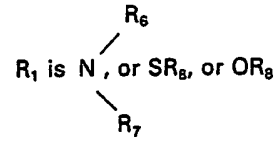
C-nucleoside	Line	Schedule (MG/KG) @ Dose	% ILS
X=NH	L—1210/O	QD × 5, D_1 @ 0.5	9.1
R_1=NH_2, R_2=H	L—1210/O	Q4D × 3, D_1 @ 0.25	17.0
R_3=R_4=R_5=OH	L—1210/MP	Q4D × 3, D_1 @ 0.4	71.8
R_5'=H	P—815/ARA C	Q4D × 3, D_1 @ 0.7	30.8
	P—815/ARA C	Q4D × 3, D_1 @ 0.4	19.8
X=S			
R_1=SCH_3, R_2=H	P—815/O	QD × 2/Q2D × 3 @ 60	71.4
R_3=R_4=R_5=OH	P—815/O	Q4D × 4, D_1 @ 40	56.3
R_5'=H			

Claims

1. Beta-glycosyl C-nucleoside compound of the formula



wherein
X is S or O



wherein R_6, R_7 and R_8 are ind pendently selected from H or alkyl of 1 to 6 carbon atoms; or

R_2 is H,
R_3 is OH,
R_4 is OH,
R_5 is OH or H,
R'_5 is H.

2. The compound of claim 1 designated 7-(β-*D*-Ribofuranosyl)-4-amino-thieno(3,2-*d*)pyrimidine.

3. The compound of claim 1 designated 7-(2'Deoxy-β-*D*-ribofuranosyl)-4-amino-thieno(3,2-*d*)pyrimidine.

4. The compound of claim 1 designated 7-(β-*D*-Ribofuranosyl)-4-amino-furo(3,2-*d*)pyrimidine.

5. The compound of claim 1 designated 7-(2'Deoxy-β-*D*-ribofuranosyl)-4-amino-furo(3,2-*d*)pyrimidine.

6. In a method for preparing the beta-glycosyl C-nucleoside compound of one of the proceeding claims, the steps of

(a) providing a blocked sugar β-ribofuranosyl C-glycoside substituted by β-dimethylaminoacrylonitrile;

(b) hydrolyzing the dimethylamino group to a hydroxyl group under conditions which do not effect the blocking groups;

(c) forming a five membered heterocyclic ring either by reaction of said hydroxyl group with N-alkyl- or aminoacetonitrile followed by a ring closure, or by mesylation of said hydroxyl group substituting the mesyl group for an oxygen or sulfur containing group suitable to effect ring closure;

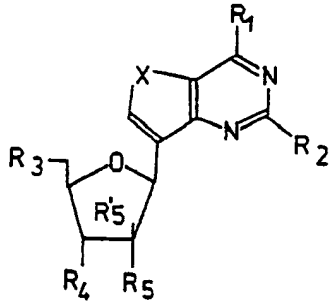
(d) separating alpha and beta isomers;

(e) forming a pyrimidine ring fused with said five-membered ring, from the beta isomer; and

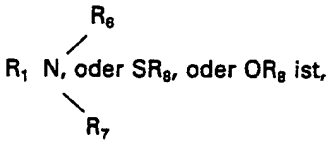
(f) unblocking the sugar.

Patentansprüche

1. Beta-Glykosyl C-Nukleosid-Verbindung mit der Formel



wobei
X S oder O ist



wobei R_6, R_7 und R_8 unabhängig ausgewählt ist aus H oder einem Alkyl mit 1 bis 6 Kohlenstoffatomen; oder wobei
R_2 H ist,
R_3 OH ist,
R_4 OH ist,
R_5 OH or H ist,
R'_5 H ist.

2. Substanz nach Anspruch 1, nämlich 7-(β-*D*-Ribofuranosyl)-4-amino-thieno(3,2-*d*)pyrimidin.

3. Substanz nach Anspruch 1, nämlich 7-(2'Desoxy-β-*D*-ribofuranosyl)-4-amino-thieno(3,2-*d*)pyrimidin.

4. Substanz nach Anspruch 1, nämlich 7-(β-*D*-Ribofuranosyl)-4-amino-furo(3,2-*d*)pyrimidin.

5. Substanz nach Anspruch 1, nämlich 7-(2'Desoxy-β-*D*-ribofuranosyl)-4-amino-furo(3,2-*d*)pyrimidin.

6. In einem Verfahren zur Herstellung der β-Glykosyl C-Nucleosid-Substanz nach einem der vorherigen Ansprüche, mit den Schritten

(a) Liefern eines mit Schutzgruppen versehenen ("blocked") Zukker-β-Ribofuranosyl-C-Glykosides, das durch β-Dimethylaminoacrylonitril substituiert ist;

(b) Hydrolisieren der Dimethylamino-Gruppe zu einer Hydroxyl-Gruppe unter Bedingungen, die die mit Schutzgruppen versehenen Gruppen nicht angreifen;

(c) Bilden ein s fünfgliedrigen h terocyclisch n Ringes ntweder durch di Reaktion der Hydroxyl-Grupp mit N-Alkyl- oder Aminoacetonitril gefolgt durch einen Ringschluß, d r durch Mesylati n der

besagt n Hydroxyl-Gruppe, indem die Mesyl-Grupp an die Stelle von iner Sauerstoff oder Schwefel enthaltenden Gruppe tritt, die ge ignet ist, einen Ringschluß zu bewirk n.

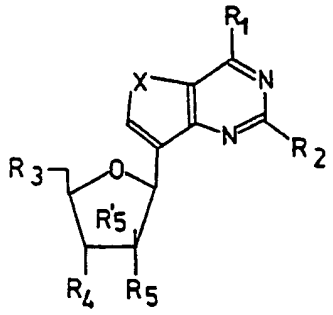
(d) Auftrennen der Alpha- und Beta-Isomere.

(e) Bilden eines Pyrimidinringes, der mit dem fünfgliedrigen Ring verschmolzen ist, aus dem Beta-Isomer und

(f) Entfernen der Schutzgruppen ("unblocking") vom Zucker.

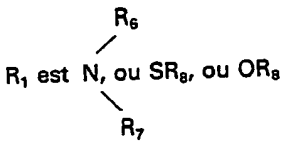
Revendications

1. Composé de type béta-glycosyl C-nucléoside, de formule



dans laquelle

X est S ou O



où R_6, R_7, R_8 sont choisis indépendamment parmi H ou un alkyle de 1 à 6 atomes de carbone; ou

R_2 est H,

R_3 est OH,

R_4 est OH,

R_5 est OH ou H,

R'_5 est H.

2. Composé suivant la revendication 1, qui est la 7-(β-*D*-ribofuranosyl)-4-amino-thiéno(3,2-*d*)pyrimidine.

3. Composé suivant la revendication 1, qui est la 7-(2'déoxy-β-*D*-ribofuranosyl)-4-amino-thiéno(3,2-*d*)pyrimidine.

4. Composé suivant la revendication 1, qui est la 7-(β-*D*-ribofuranosyl)-4-amino-furo(3,2-*d*)pyrimidine.

5. Composé suivant la revendication 1, qui est la 7-(2'déoxy-β-*D*-ribofuranosyl)-4-amino-furo(3,2-*d*)pyrimidine.

6. Dans un procédé pour la préparation du composé béta-glycosyl C-nucléoside suivant l'une des revendications précédentes, les opération de

(a) prépartion d'un sucre bloqué de type β-ribofuranosyl C-glycoside substitué par β-diméthylamino-acrylonitrile;

(b) hydrolyse du groupe diméthylamino en un groupe hydroxyle dans des conditions qui n'affectent pas les groupes de blocage;

(c) formation d'un anneau hétérocyclique à cinq éléments, par réaction dudit groupe hydroxyle avec un groupe N-alkyl- ou aminoacétonitrile suivie par une fermeture du cycle, ou bien par mésylation dudit groupe hydroxyle substituant le groupe mésyle à la place d'un groupe contenant de l'oxygène ou du soufre, de manière à effecteur la fermeture du cycle;

(d) séparation des isomères alpha et béta;

(e) formation d'un anneau pyrimidine fusionné avec ledit anneau à cinq éléments à partir de l'isomère béta; et

(f) élimination du blocage du sucre.